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ACUTE DIFFUSE GLOMERULAR NEPHRITIS

STUDY OF NINETY-FOUR CASES WITH SPECIAL CONSIDERATION OF THE STAGE OF TRANSITION INTO THE CHRONIC FORM

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During the past fifteen years intensive investigations of chronic nephritis have brought about remarkable changes in the conception of many of its features. The disturbances of mineral, protein and water metabolism and their relationship to symptoms as well as to histologic changes have been worked out in some detail. The studies of acute nephritis, especially in the adult, are comparatively few, and this disease is less well understood than the chronic form.

It is almost universally accepted that chronic glomerular nephritis develops as the result of an acute attack which remains unhealed. Yet no extended experience with the chronic form is necessary to show that in most cases a history of an acute attack is lacking. In many cases the acute attack is so mild that the disease passes unnoticed, and the first evidence of a damaged kidney appears months or years later with the development of the signs and symptoms of the chronic stage. If the prevailing opinion is accepted that acute diffuse glomerular nephritis is characterized by the sudden onset of hematuria, hypertension and edema, many cases of the acute form will continue unrecognized until they pass into the chronic phase. Such a classic picture of hematuria, hypertension and edema develops only after an abrupt attack of acute nephritis which, at least temporarily, overwhelms the function of the kidney. Milder attacks may produce no such syndromes, but are capable of producing a lesion which just as often leads to the chronic form. As has been pointed out by many writers, and especially stressed by Volhard,[1] Longcope and his associates,[2] Lyttle and Rosenberg[3] and

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1. Volhard, F., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, p. 2, p. 1179.

2. Longcope, W. T.; O'Brien, D. P.; Guire, J. M.; Hansen, O. C., and Denny, R. R.: Relationship of Acute Infections to Glomerular Nephritis, J. Clin. Investigation **5**:7 (Dec.) 1927.

3. Lyttle, J. D., and Rosenberg, L.: Prognosis of Acute Nephritis in Childhood, Am. J. Dis. Child. **38**:1052 (Nov.) 1929.

Bell and Hartzell,[4] scarlet fever and severe streptococcic infections of the throat are considered the most important causes of acute glomerular nephritis. Yet milder grades of infections of the upper respiratory tract, which frequently are not suspected as etiologic factors, may produce severe nephritis. Occasionally the only evidence of an attack of nephritis is found on examination of the urine, and it may be missed unless urinalysis is repeated frequently. If specimens of urine were examined as carefully and as often during the course of all infections of the upper respiratory tract as during scarlet fever, many more cases of acute nephritis would be disclosed.

Following the acute attacks of either the severe or the mild form, there is often a period of quiescence, in which the renal lesion heals completely or passes insidiously into the chronic phase. It is in this stage of transition that the patient usually feels well and is often regarded as cured, and attention to the details of diagnosis and treatment is neglected. The result is that the patient lives comfortably, not knowing that anything has gone wrong with the kidney until the chronic form supervenes months or years later, when little or nothing can be done to stop the downward progress of the disease. While the disease is still in the transitional stage it is of great importance to be able to determine, in a given case, whether the acute nephritic lesion is healing or becoming chronic. There is good reason to believe that if the true course of the disease is known and vigorous treatment instituted in this stage, the unfavorable sequelae may be prevented, for it is at this period that chronic glomerular nephritis may become inevitable, and the destiny of the kidney is determined.

In this report special emphasis is laid on the less pronounced cases of acute nephritis and on those in the stage of transition. We have analyzed ninety-four cases of acute diffuse glomerular nephritis admitted to the clinic of the hospital and dispensary for the treatment of nephritis during the years 1924-1934. The patients admitted during the period from 1929 to 1934, however, were more completely studied, and their cases are more fully reported here. The purposes of this study are as follows: (*a*) to review the general features of our cases as they were seen chiefly in adults; (*b*) to show that during the course of mild infections such as the common cold, when special attention is paid to the urinary findings, unsuspected nephritis may be diagnosed, and that the classic syndromes of hematuria, hypertension and edema need not be present; (*c*) to give particular consideration to the cases in the stage of transition during which healing or a state of chronicity occurs, and, finally (*d*) to show that the blood urea clearance test and

4. Bell, E. T., and Hartzell, T. B.: Etiology and Development of Glomerulonephritis, Arch. Int. Med. **29**:768 (June) 1922.

the sedimentation rate for erythrocytes in conjunction with the tests more commonly used, aid in deciding whether the renal lesion is healing or becoming chronic.

ANALYSIS OF THE CLINICAL DATA

In this series there was wide variation in the age incidence, as shown in table 1, in which a comparison of the ages of the patients is given. It may be noted that fifty-nine of ninety-four cases, or 62.7 per cent, occurred in patients between the ages of 10 and 30 years, while in thirty-five cases the patients were past 30 years of age. The table emphasizes the fact that this is not a childhood group, but predominantly a series of adults with nephritis. Also, it is shown that of fifty-nine patients under 30 years of age, twelve or 20 per cent, died, as compared with fifteen, or 42 per cent, of thirty-five patients in the group over

TABLE 1.—*Comparison of Ages of Ninety-Four Patients with Acute Glomerular Nephritis*

Age, Years	Number of Cases	Recovered		Became Chronic		Died	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
0 to 10 11 to 20 21 to 30	50	31	52.54	16	27.12	12	20.34
31 to 40 41 to 50 51 to 60	35	16	45.71	4	11.43	15	42.86
Total	94	47	50.00	20	21.28	27	28.72

30 years. Of twelve patients under the age of 10 years, seven recovered; the condition of three became chronic, and two died (table 2). Although acute glomerular nephritis may occur at any age, it is rare after the age of 50 and common in children and adolescents. The higher incidence among young patients is, without doubt, properly attributed to the greater frequency of diseases of the upper respiratory tract.

The sex of the patients appeared to be inconsequential. As shown in table 2, there were fifty-one males and fifty-three females. The age, sex incidence and final outcome are arranged according to decades.

It has been pointed out from time to time that the mortality rate is higher among adults with acute nephritis than in children. Our mortality rate was highest among the patients in the age group from 40 to 50 years, as six of twelve patients in this group died. Between the ages of 30 and 40 years, eight of twenty patients died, while in the age group from 20 to 30 years, four of twenty-one patients died. Twelve cases occurred in patients between 5 and 10 years of age, and of these two died. The outcome in relation to age and sex incidence is arranged in table 3. The average age of patients who died was

29 years, as compared with 20 and 24 years, respectively, for those in whom the condition became chronic or who recovered. Of the entire series of patients 47, or 50 per cent, recovered completely; in twenty, or 21 per cent, the condition became chronic, and 27, or 28 per cent, died.

The form of acute nephritis complicating scarlet fever has been taken as a model of acute diffuse glomerular nephritis. Twenty years ago scarlet fever was considered the chief cause of acute diffuse

TABLE 2.—*Age and Sex Incidence in Ninety-Four Cases of Acute Glomerular Nephritis*

Age	Number	Per Cent of Total	Number of Males	Per Cent of Total	Number of Females	Per Cent of Total	Number Recovered	Per Cent of Total	Number Became Chronic	Per Cent of Total	Number Died	Per Cent of Total
0 to 10	12	12.77	7	7.45	5	5.32	7	7.44	3	3.19	2	2.13
11 to 20	26	27.66	11	11.70	15	15.95	12	12.77	8	8.51	6	6.38
21 to 30	21	22.33	8	8.51	13	13.83	12	12.77	5	5.32	4	4.25
31 to 40	20	21.27	11	11.70	9	9.57	9	9.57	3	3.19	8	8.51
41 to 50	12	12.77	11	11.70	1	1.06	5	5.32	1	1.06	6	6.38
51 to 60	3	3.20	3	3.20	0	0	2	2.13	0	0	1	1.06
Total	94	100.00	51	54.25	43	56.38	47	50.00	20	21.28	27	28.72

TABLE 3.—*Outcome in Relation to Age and Sex Incidence*

	Number	Per Cent of Total	Number of Males	Average Age of Males, Years	Number of Females	Average Age of Females, Years	General Average Age, Years	Youngest Patient	Oldest Patient
Recovered	47	50.00	29	27.72	18	21.77	24.75	5	59
Became chronic	20	21.28	4	18.00	16	22.43	20.21	8	46
Died	27	28.72	19	34.57	8	23.50	29.03	7	57
Total number of cases	94	100.00	52	26.76	42	22.57	24.66	5	59

nephritis. More recently, however, investigations have shown that other forms of infections, especially those of the upper respiratory tract, overshadow scarlet fever as the chief cause of acute nephritis. As shown in table 4, fifty-four, or 57.4 per cent, of the cases were caused by the common cold, tonsillitis and pneumonia. The onset of acute nephritis was preceded by scarlet fever in only two cases. The infrequency of scarlet fever as an etiologic agent in this series is surprising; but we believe it may be explained by the fact that our cases were gathered in a general hospital to which few patients with contagious diseases are admitted.

At the head of the list of etiologic factors are the common cold and influenza. They accounted for twenty-six cases, or 27.6 per cent. Pneumonia occupies an important place in our list, for eight, or 8.5 per cent, of our cases were caused by it. This comparatively high

incidence may be explained by the fact that we have carefully watched these patients for evidences of acute nephritis. We have excluded cases of so-called febrile albuminuria.

Within recent years the part played by the toxemia of pregnancy in the production of acute nephritis has been emphasized by various authors (Mussey and Keith,[5] Bell[6] and Baird and Dunn[7]). These writers have expressed the belief that acute glomerular nephritis is one of the manifestations of the toxemia of pregnancy. We have selected sixteen cases from among a large number of patients with eclampsia to illustrate the acute nephritic syndromes commonly observed. Our autopsy studies in connection with these cases lead us to believe that acute diffuse glomerular nephritis due to eclampsia is practically the same as that due to other causes.

TABLE 4.—*Etiology of Ninety-Four Cases of Acute Glomerular Nephritis*

Causes	Number of Cases	Per Cent of Total	Number Recovered	Per Cent of Total	Became Chronic	Per Cent of Total	Number Died	Per Cent of Total
Common cold; influenza	26	27.66	12	12.78	7	7.44	7	7.44
Cold (exposure)	1	1.06	1	1.06	0	0	0	0
Sore throat; tonsillitis	20	21.27	14	14.89	3	3.20	3	3.20
Scarlet fever	2	2.13	0	0	1	1.06	1	1.06
Pneumonia	8	8.51	2	2.13	2	2.13	4	4.25
Other infections	14	14.89	8	8.51	0	0	6	6.38
Toxemia of pregnancy	16	17.03	6	6.38	7	7.44	3	3.20
Unknown	7	7.45	4	4.25	0	0	3	3.20
Total	94	100.00	47	50.00	20	21.27	27	28.73

The five classic clinical syndromes which characterize the chronic stage of nephritis, as outlined elsewhere by one of us,[8] are applicable to the acute phase. They are: (*a*) the urinary syndrome, (*b*) hypertension, (*c*) edema, (*d*) retention of nitrogen and (*e*) uremia. As in the chronic stage, it is seen in the acute that not all the syndromes need be present at the same time; at times one or another develops and dominates the clinical picture and then disappears, to reappear at a later date or never to return. In every case the urinary syndrome was present when the diagnosis was made. Some authors, notably Kylin,[9] have reported that hypertension, edema and even uremia may precede

5. Mussey, R. D., and Keith, N. M.: Significance of Nephritis in Pregnancy, J. A. M. A. **91**:2044 (Dec. 29) 1928.

6. Bell, E. T.: Renal Lesions in Toxemias of Pregnancy, Am. J. Path. **8**:1 (Jan.) 1932.

7. Baird, D., and Dunn, J. S.: Renal Lesions in Eclampsia and Nephritis of Pregnancy, J. Path. & Bact. **37**:391 (Sept.) 1933.

8. Murphy, F. D.: Syndromes of Chronic Nephritis and Their Corresponding Morphological Changes, Internat. Clin. **2**:45 (June) 1929.

9. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926, p. 57.

albuminuria. We have never observed this. The urinary syndrome, as shown in table 5, was present in every case, and in many cases it was the only one present when the diagnosis was made. Reliance on the urinary changes was necessary to a great extent in many of our cases, because other classic syndromes, as edema, hypertension and retention of nitrogen, were absent. Disturbances of urination, characterized by frequency of micturition and oliguria or occasionally complete anuria, were foremost among the symptoms at the onset, and at times were the only symptoms present. It was necessary, occasionally, to differentiate between febrile albuminuria and genuine acute nephritis in some of the milder cases. Frequently simple albuminuria developed and continued during the period of high fever, while acute glomerular nephritis set in after the chief symptoms of the causal disease subsided. In cases of febrile albuminuria, few or no red blood cells, pus cells and granular casts were found; while in nephritis these elements were prominent features. Changes in the urinary output, as oliguria or anuria, were rarely present in febrile albuminuria and were constant in nephritis. Also, in febrile albuminuria the albumin diminished rapidly with the subsidence of fever; but in acute nephritis the urinary syndrome continued for weeks after the fever disappeared. The amount of albumin excreted in twenty-four hours was so variable that we concluded that little or no significance could be attached to the quantity passed in the acute cases. Likewise, hematuria varied greatly, not only from patient to patient, but from day to day in the same patient. In some cases the urine was bloody from the onset, while in others only an occasional red cell was found during the acute stage. From such experiences we do not believe, as some advocate, that the term acute hemorrhagic nephritis should be used synonymously with acute diffuse glomerular nephritis. Gross hematuria was present in thirty-six cases, or 38 per cent. Red blood cells were in the sediment in varying amounts at some period of the acute process in every case. However, the number of red blood cells and of casts or the amount of albumin bore no relationship to the severity of the disease. Some of our cases in the early stages showed pronounced hematuria, and so were diagnosed as cases of focal glomerular nephritis, but we found on further observation that genuine diffuse glomerular nephritis existed.

Table 5 shows that hypertension was present in seventy-four cases, or 78.7 per cent. Its presence or absence did not appear to influence greatly the ultimate outcome. Rising blood pressure or hypertension that tends to persist after other signs have subsided is an unfavorable sign. Our observations tend to substantiate the opinion that persistent hypertension is indicative of an unhealed nephritic lesion. Cerebral hemorrhage is thought to be rare in acute nephritis, yet in this series it occurred twice. In each case the blood pressure was only moderately elevated, and the patients were under 20 years of age.

Associated at times with hypertension are changes in the fundus oculi. In this series neuroretinopathies were found in only seven patients with excessive hypertension. Frequently, the excessive hypertension was complicated by convulsions. The changes in the eyegrounds varied from lesions of mild degree, characterized by slight retinal edema and moderate constriction of the retinal arteries, to the typical picture of so-called nephritic retinitis, consisting of edema of the retina, choked disks, hemorrhages along the course of the retinal arteries, narrowed and partially obscured retinal arteries and white patches. Although some observers, as Fishberg,[10] have pointed out that the presence of nephritic neuroretinopathy indicates a serious prognosis, we cannot

TABLE 5.—*Syndromes Occurring in Ninety-Four Cases of Acute Glomerular Nephritis*

Syndromes	Recovered (47)		Became Chronic (20)		Died (27)	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Urinary	47	100.00	20	100.00	27	100.00
Hypertension	35	74.47	15	75.00	24	88.80
Edema	32	68.09	15	75.00	15	55.55
Retention of nitrogen	31	65.96	13	65.00	23	85.19
Uremia	6	12.77	2	10.00	20	74.07
Genuine	0	0	0	0	14	51.85
Convulsive	6	12.77	2	10.00	6	22.22

TABLE 6.—*Causes of Death in Twenty-Seven Cases of Acute Glomerular Nephritis*

Causes	Number of Cases	Per Cent
Uremia	20	74.07
Heart failure	3	11.11
Pneumonia	3	11.11
Other infections	1	3.71
Total	27	100.00

reach that conclusion from our observations, as some of our most dramatic recoveries were among the patients having convulsions and neuroretinopathies.

Various degrees of myocardial insufficiency were found in fifteen of the ninety-four cases observed, and, as seen in table 6, in three of the twenty-seven fatal cases death was caused by heart failure. Failure of the left ventricle was observed in these cases, and was usually associated with excessive hypertension and convulsions. During the convulsion the heart was frequently observed to be on the verge of collapse, only to return to a normal state with recovery from the convulsive attack. As emphasized by Levy,[11] hypertension frequently causes mild

10. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934.

11. Levy, I. T.: Cardiac Response in Acute Diffuse Glomerular Nephritis, Am. Heart J. **5**:279 (Feb.) 1930.

degrees of heart failure, which often pass unnoticed. Although heart failure in our group usually was associated with hypertension, this was not always true. In one fatal case the blood pressure was not elevated, yet the patient died of failure of the left side of the heart. A report of this case is given because it illustrates several features we wish to emphasize: first, that left ventricular failure may occur in acute nephritis with no elevation of the blood pressure; second, that in acute diffuse glomerular nephritis there may be too few red blood cells in the urine to warrant the term "hemorrhagic," and, finally, that acute glomerular nephritis may set in rapidly following exposure to cold and the onset of an infection of the upper respiratory tract.

CASE A.—A white man, aged 33, a city fireman, entered the hospital on Aug. 8, 1933. He had always been in splendid health. On August 4, he was drenched with water, and a severe cold developed in the head and chest. He was confined to bed on August 6 and 7. On August 8, he felt worse, and had not urinated for twenty-four hours. On catheterization about 15 cc. of clear urine was obtained. Analysis revealed: albumin 4 plus, from 8 to 10 pus cells, 8 to 10 granular casts and from 2 to 4 red blood cells per field. The nonprotein nitrogen was 210 mg. per hundred cubic centimeters and the creatinine was 14 mg. The blood pressure, which had always been normal, was 132 systolic and 90 diastolic. Efforts to bring about diuresis failed. On August 9, he became dyspneic, and râles began to gather in the bases of both lungs. During the day the signs of left ventricular failure became more pronounced, and toward evening well developed pulmonary edema with the typical frothy expectoration set in. The blood pressure dropped to 100 systolic and 70 diastolic, and a definite gallop rhythm developed. Complete anuria persisted. Heart failure rapidly increased in severity, and the patient died the next morning.

At autopsy the kidneys were large, white and smooth, the right one weighing 225 Gm. and the left, 195 Gm. The capsules stripped with ease, and the renal substance bulged out through the opening made in the true capsule. No hemorrhagic areas were seen on opening the kidney. Microscopically the glomerular tufts were uniformly enlarged, practically filling Bowman's space in most areas. The capillaries of the tufts were practically bloodless throughout. The lumens were occluded by swelling of the endothelial cells and polymorphonuclear leukocytes. The endothelial cells of the capillaries were considerably increased in number in some sections; in others this was not so noticeable. In the capsular spaces, exudate containing pus cells but no red blood cells had accumulated. The epithelial cells of the proximal and distal convoluted tubules were swollen, and appeared to be undergoing granular degeneration. Very little fat was found with the fat stains, and no doubly refracting lipoids were seen with the polarizing microscope. The blood vessels were normal.

Every patient in our series having uremia of the convulsive type had hypertension before convulsions set in. As a rule the blood pressure was higher in these cases than in others, and convulsions developed at the height of the pressure. The association of hypertension and the onset of convulsions is so striking that we believe a cause-and-effect relationship exists.

Edema was never a severe complication in this group of cases. Usually it was slight, with puffiness about the eyes; occasionally it was more pronounced, with ascites and fluid in other cavities, but it rarely assumed the proportions of generalized anasarca. Edema developed in sixty-two cases, or 65.9 per cent. It was present in thirty-two, or 68.09 per cent, of the patients who recovered, while it occurred in fifteen, or 75 per cent, of those in whom the condition became chronic and in fifteen, or 55.5 per cent, of those who died. There was no relationship between the degree of edema and the prognosis. As shown in table 5, edema was least often present in fatal cases and most often in those becoming chronic. In many of the cases studied the amount of plasma proteins was determined. There seemed to be no relationship between the quantity of plasma protein and the edema, as is so marked a feature of chronic nephritis with edema. In most cases the amount of total protein and of albumin and globulin was normal. In most cases with edema the plasma protein level was normal; occasionally edema was associated with a reduction of the total plasma protein to 6 Gm. per hundred cubic centimeters or below, with an albumin level between 3 and 4 Gm. per hundred cubic centimeters. Rarely, a decrease of protein was found when no edema prevailed.

Estimations of the blood cholesterol content were done in seventy-two of the ninety-four cases. In eighteen cases there was a cholesterol content above 200 mg. There was no relationship between the content of blood cholesterol and the fatal outcome. In the group whose condition became chronic there was a tendency of the content of the blood cholesterol to rise gradually. Retention of nitrogen was present in sixty-seven cases, or 71.2 per cent. When anuria set in suddenly the rise in nonprotein nitrogen usually occurred promptly. The degree of retention of nitrogen did not alter the prognosis, but with an elevated nonprotein nitrogen value that remained higher than normal the outlook for complete recovery was unfavorable. An initial abrupt rise in nonprotein nitrogen was frequently followed by prompt recovery, while other cases with little or no rise in the blood nonprotein nitrogen ended fatally. A rising nonprotein nitrogen level, as shown by repeated examinations, indicated a failing kidney and a poor prognosis.

The uremia syndrome occurred in twenty-eight cases, or 29.7 per cent. In this analysis the term uremia was used to embrace two rather different clinical syndromes. Although such use of the term uremia may not be acceptable to all, it has long been used in the sense in which it is employed here. Two forms of uremia were recognized, the genuine form and the convulsive or so-called false uremia of some writers. The convulsive form occurred in six, or 12.7 per cent, of the patients who recovered; in two, or 10 per cent, of those with conditions becoming chronic, and in six, or 22.2 per cent, of those who died. This form

was always associated with hypertension, headache and visual disturbances, and frequently was accompanied by edema. Temporary blindness was seen to come on before or during the attack and rapidly clear up with the subsidence of hypertension. The hypertension is believed to be the chief cause in this type. The retention of nitrogen and anuria appeared to be unrelated to this form of uremia. The hypertension already present rose sharply before the attack. As a rule, those with convulsive uremia alone recovered. When anuria or oliguria developed, a combination of genuine and convulsive uremia was seen to occur. In sharp contrast to the convulsive form is the genuine or true uremia. This form needs no explanation here, as it is the direct result of renal insufficiency. Genuine uremia occurred in fourteen cases, and death followed in each instance (table 5). These were cases in which renal failure developed, and treatment failed to bring about diuresis.

Although the five classic syndromes of nephritis characterize the acute as well as the chronic stage of glomerular nephritis, all except the urinary syndrome may be absent, especially in the earlier stages and in milder forms of the disease. Not all the syndromes may be present at one time; sometimes one or the other appears and dominates the picture for a while and then disappears, to reappear at some later date or never to return at all.

STAGE OF TRANSITION

When the acute attack is severe, the diagnosis, clinical course and treatment are usually well defined. But after the acute phase is over, which usually occurs within a period of six weeks, the problem frequently arises as to whether the renal lesion has completely healed or has subsided temporarily, only to progress into the chronic stage later on. Acute diffuse glomerular nephritis may take several courses: 1. The patient may die in the acute attack. 2. Chronic nephritis may develop. 3. Complete healing may occur. 4. Albuminuria may persist in small quantities for years, although the patient may be clinically cured. This is called latent albuminuria. We know that the severity of the acute attack has little influence on the subsequent course, as in some of the most severe attacks of acute nephritis healing occurred promptly, while a mild attack might be followed shortly by the chronic stage. In the type of case with a poorly defined acute stage, with symptoms so mild that they rarely attract attention, the condition of the patient who usually feels quite well may pass unrecognized and untreated into the healed stage, or progress insidiously into the chronic form.

It is in the period of transition from the acute attack into the healed stage on the one hand and into the chronic phase on the other that the ultimate fate of the patient is determined. Our experience with

this series of cases leads us to believe that the danger of oncoming chronic nephritis may be recognized in this transitional stage and that more vigorous and prolonged treatment may bring about complete quiescence of the disease. The knowledge at least of the presence of the unhealed lesion is of considerable importance, as it leads to more caution in avoiding mild infections and to more diligence in treating them. A sense of false security may develop during this time because of the patient's apparent well-being, and ordinary tests show the kidneys to be well on the road to complete healing. At times, in spite of the most careful examinations, it is difficult to decide whether the renal lesion is healing or becoming chronic. In some cases, the chronic form appears many years after all the ordinary tests indicated that healing was taking place.

The functional tests more commonly used, such as the phenolsulphonphthalein test, and the degree of retention of nitrogen have not helped greatly in deciding this question. Such tests are of value when the renal function is decidedly reduced. In cases of the type under consideration more delicate tests have been shown to be of greater value. The functional tests show only the degree of loss of reserve capacity of the kidneys, and do not indicate whether or not an inflammatory lesion persists. It seems possible for a pathologic lesion to be active in the kidney and to be associated with normal function. In attempting to determine the degree of activity of the inflammatory lesion in these transitional cases, we have found that no test alone is a reliable guide in every case.

Several methods have been used in approximating this information, and we found that a combination of these results forms a more adequate prognostic indication that any test taken alone. The blood pressure, a study of the urinary sediment, the degree of anemia, the amount of plasma proteins and the dilution concentration test of Volhard, in general, have been of considerable value, but the blood urea clearance test and the sedimentation rate of the erythrocytes have been of particular help. These measures will be presented seriatim, and the last two will be discussed more fully than the rest, because they have been found to be the most accurate of all in estimating the degree of activity in the renal lesion. 1. An elevation of the blood pressure indicates active glomerular damage. Normal pressure, however, does not signify a healed lesion, for some patients, especially those with a mild attack, have no rise in blood pressure. 2. Gradually diminishing albuminuria points toward a healing process. But in some cases there was a mere trace of albumin, and subsequently chronic nephritis developed. The number of red blood cells and granular casts in the sediment makes a more reliable guide. A decrease in the number of these elements points toward healing, but occasionally the sediment may contain no

cells, and yet the chronic phase may ensue. 3. Anemia (below less than 3,500,000 red blood cells) implies a progressive renal breakdown, but this is an unreliable guide, for anemia practically never appears in mild cases. 4. A fall in the plasma protein values is a sign of a progressive renal lesion, while if the plasma protein values remain normal the case usually progresses satisfactorily. It was observed that the decrease was not commensurate in all cases with the amount of protein in the urine; other factors appear to influence the plasma protein values. 5. The concentration and dilution test of Volhard was found to be very reliable. Impaired concentration in most cases pointed to an unhealed progressive lesion. This important test requires considerable cooperation from the patients; however, we have found it to be of great help in arriving at a proper prognosis. 6. Of all tests the blood urea clearance was the most accurate; yet, in a few cases it was found to be undependable. 7. Finally, the erythrocyte sedimentation rate proved to be an important aid in determining the degree of activity of the renal lesion. In this series we have paid particular attention to the last two tests, and therefore we shall discuss them more fully than the others. Summaries of the data on all the cases which became chronic are given in table 7, and similar data are given in table 8 on ten of the forty-seven cases which went on to recovery. These ten were selected because on them we have been able to do more complete work and have a more adequate follow-up than on the others.

The blood urea clearance test, as described by Möller, McIntosh and Van Slyke,[12] has been used regularly in the study of our cases. A discussion of the technic of the test seems unnecessary, for, subsequent to the original description, it has been used widely and reported on by such workers as Van Slyke, McIntosh, Möller, Hannon and Johnston,[13] Cantarow and Ricchiuti[14] and Bruger and Mosenthal,[15] all of whom have given detailed descriptions of the procedure. In this report the figures for blood urea clearances are given in a per cent of the normal mean, which, according to Van Slyke and his associates, is 54 cc. of blood per minute for the normal average standard clearance and 75 cc.

12. Möller, E.; McIntosh, J. T., and Van Slyke, D. D.: Studies of Urea Excretion: II. Urine Volume and Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427 (Dec.) 1928.

13. Van Slyke, D. D.; McIntosh, J. F.; Möller, E.; Hannon, R. R., and Johnston, C.: Studies of Urea Excretion: VI. Comparison of the Blood Urea Clearance with Other Measures of Renal Function, J. Clin. Investigation **8**:357 (April) 1930.

14. Cantarow, A., and Ricchiuti, G.: Urea Clearance Test in Pregnancy, Arch. Int. Med. **52**:637 (Oct.) 1933.

15. Bruger, M., and Mosenthal, H. O.: Urea Clearance Test as an Index of Renal Function: I. Studies of Normal Subjects, Arch. Int. Med. **50**:351 (Sept.) 1932.

TABLE 7.—*Essential Data in Twenty Cases of Acute Glomerular Nephritis Which Became Chronic*

TABLE 7.—*Essential Data in Twenty Cases of Acute Glomerular Nephritis Which Became Chronic*

Case	Age	Sex	Etiology	Date	Urinary Observations				Blood Chemistry				Edema	Blood Pressure		Uremia	Blood Urea Clearance	Sedimentation Rate	
					Albumin	Red Blood Cells	White Blood Cells	Casts	Specific Gravity	Non-protein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.		Systolic	Diastolic			1st Hour	2d Hour
1	16	F	Tonsillitis	12/28/32	++++	+++	++	+	1.016	34.8	1.5	320	+++	128	88	Neg.	47	27	58
				3/29/33	++++	++	+	0	1.011	38.2	1.6	355.4	++++	150	80	0	27	15	30
2	23	F	Sore throat; tonsillitis	7/ 9/26	+++	+++	+++	++	1.030	31.08	...	.....	0	90	55	0			
				8/28/26	+	+	+	0	.....	.. .	...	.....	0	188	98	0			
3	32	F	Toxemia of pregnancy	7/ 9/32	+++	+	+++	0	1.018	40.3	1.9	250.0	++	162	104	0	22	35	73
				11/ 1/32	+++	++	+++	0	1.018	47.2	1.8	220.3	+++	200	140	Convulsions	28	46	85
4	14	F	Common cold; influenza	11/ 8/30	++++	+++	++	Occ. +	1.012	54.0	1.9	227.0	++++	154	88	0	15		
				7/13/31	++++	+	+	++	.....	37.0	...	.....	..	140	100	...	45		
5	16	F	Sore throat; tonsillitis	12/10/32	++++	+	+++	0	1.010	28.5	1.4	142.8	++++	132	88	0	44	19	24
				4/ 2/33	++	+	++	+ Occ.	1.008	27.7	1.5	238.1	++++	132	80	0	26	38	56
6	13	F	Tonsillitis	7/13/31	++++	++	++++	++	1.015	39.5	1.5	189.3	+++	148	100	0	65	52	82
				4/ 7/32	Trace	+	++	0	1.016	37.7	1.4	178.5	..	130	70	0	58	48	90
7	37	F	Toxemia of pregnancy	4/ 5/33	++++	+	++	0	1.024	45.4	1.4	400.0	+	200	120	0	56	42	81
				6/20/33	++++	0	+	+++	1.017	33.7	1.6	200.0	..	190	115	0	32	16	37
8	17	M	Sore throat; tonsillitis	6/13/32	++++	++++	++	+	1.016	67.4	2.1	181.8	++	156	68	0	65	61	88
				9/11/33	++++	+++	+++	++	.....	.....	...	.....	++	155	90	...	25		
9	9	F	Pneumonia	3/18/33	++++	+++	++	++	1.012	150.0	6.5	225.0	++++	110	80	0	58	21	50
				4/18/33	++++	++++	++++	0	1.011	36.1	1.5	184.1	..	150	100	...	30	24	48
10	26	F	Toxemia of pregnancy	5/ 7/32	++++	+	++	++	1.019	35.0	1.5	181.9	+++	145	120	0			
				3/ 6/33	+	+	0	++											
11	24	F	Toxemia of pregnancy	1/ 1/30	++++	++++	+++	++	.....	29.2	1.6	253.0	+	200	136	0	..	110	122
				10/ 2/33	+	+	0	++	.....	....	...	.....	..	160	90				
12	8	M	Scarlet fever	2/ 7/25	+++	+++	++	+	1.022	....	...	.....	0	132	92	0			
				6/12/25	+++	+	++	++	1.016	52	2.4	.....	..	124	90	0			
13	12	M	Sore throat; influenza	3/ 6/24	++	0	+	0	1.025	..	...	.....	++	115	80	0			
				9/18/24	+	0	0	0	1.017	15	2.0	320	0	115	80	0			
14	22	M	Common cold; influenza	3/ 5/28	++++	+++	+++	+++	1.026	48	2.5	212	++	150	100	0	..	36	66
				6/ 1/28	+	++	++	+	1.015	60	3.0	300	0	148	104	0	..	45	70
15	18	F	Pneumonia	11/ 7/30	+++	++	+++	0	1.018	42	1.8	190	+	130	82	0	60	50	80
				1/29/31	+	+	++	0	1.010	38	2.0	...	0	142	100	0	45	38	65
16	13	F	Sore throat; tonsillitis	7/ 3/26	++	+	++	+	1.028	32	1.2	...	++	110	80	0	..	40	60
				9/20/26	0	..	..	0	1.022	36	1.6	220	0	110	50	0	..	50	75
17	38	F	Toxemia of pregnancy	4/12/32	+++	++	+++	++	1.024	40	2.8	280	+	190	115	0	32	28	50
				9/ 2/32	++	++	+	+	1.015	72	3.4	310	+	180	120	Convulsion	14	45	95
18	27	F	Toxemia of pregnancy	4/ 6/31	++++	++	+++	+	1.020	..	...	...	++	160	110	0	38	36	52
				8/20/31	++	++	++	+	1.010	60	3.0	216	+	142	92	0	26	42	88
19	19	F	Toxemia of pregnancy	2/ 2/27	+++	+	++	0	1.024	46	2.1	200	+++	158	100	0			
				5/10/27	+++	+	0	0	1.018	..	...	...	+	160	100				
20	25	M	Tonsillitis; sore throat	10/12/31	++	+++	++	++	1.025	25	2.0	184	++	140	85	0	38	40	65
				1/ 5/32	++	++	+	0	1.020	38	2.2	216	0	156	96	...	18	60	90

for the average maximum clearance. In determining whether the acute condition is healing or progressing into the chronic stage the blood urea clearance has definite value. It is probably the most delicate of any of the tests of renal function, and it reveals early functional impairment considerably sooner than the usual tests employed. Furthermore, it was pointed out by Van Slyke and his co-workers [16] that one may interpret the blood urea clearance as a measure of the proportion of glomerular tissue still functioning and that a fairly accurate impression may be obtained concerning the rate of progress of the renal lesion itself. As shown in table 7, no case becoming chronic maintained a normal urea clearance. In a few, as in cases 1, 7, 8 and 15, the urea clearance was satisfactory during the early periods of the disease, ranging from 40 to 60 per cent of normal, while in others the initial observations revealed urea clearances as low as 10 per cent of normal. When the initial blood urea clearance was satisfactory in cases becoming chronic, repeated examinations showed a tendency toward a drop in the percentage; while in the cases in which the initial test showed a decided lowering of urea clearance ranging from 15 to 30 per cent of normal, a rise to normal was not found in the stage of transition into the chronic form. This does not mean that the percentage of clearance made no rise in some cases which became chronic. In case 4, for example, the initial clearance was 15 per cent, followed by a rise to 45 per cent; yet the condition continued toward the chronic stage.

In the group of cases which went on to the healed stage as a rule the urea clearances were depressed during the early periods of the acute stage, while in later periods the clearances tended to increase (table 8). In some, as in cases 22 and 28, the clearances were normal and remained so, but in most cases in this group an early depression showed, followed after several weeks of rather marked fluctuations by a gradual rise to normal. We wish to emphasize that clearance tests done during the early stages of acute nephritis do not tell whether the outcome will be favorable or unfavorable. However, repeated tests over a period of months show whether the general trend is toward healing or toward chronicity. This, nevertheless, is no ironclad rule, for there were cases in which the clearances remained normal during the early months, and yet the condition went on to the chronic stage, as seen in case 6, table 7. In this case the sedimentation rate was more serviceable as a prognostic guide than the blood urea clearance test. Because of its importance a more detailed presentation is given here.

16. Van Slyke, D. D.; Stillman, E.; Möller, E.; Eggert, E. W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Course of Different Types of Bright's Disease and on the Resultant Changes in Renal Anatomy, Medicine **9**:257 (Sept.) 1930.

TABLE 8.—*Essential Data in Ten Cases of Acute Glomerular Nephritis in Which Recovery Occurred*

Case	Age	Sex	Etiology	Date	Urinary Observations				Specific Gravity	Blood Chemistry			Edema	Blood Pressure		Uremia	Blood Urea Clearance	Sedimentation Rate	
					Albumin	Red Blood Cells	White Blood Cells	Casts		Non-protein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.		Systolic	Diastolic			1st Hour	2d Hour
21	24	M	Common cold;	12/14/32	++++	+++	+++	++	1.018	53	3.2	526.2	+++	152	102	Neg.	23	45	60
			influenza	3/30/33	+	0	0	0	1.024	32	1.4	242.7	0	132	100		50	12	18
22	40	M	Influenza;	4/20/31	++++	++	+++	++	1.017	48	2.0	.....	+	120	70	Neg.	58	24	32
			common cold	8/ 9/31	0	++	++	++	.....	45	1.2	.....	0	120	80		90	8	12
23	28	M	Sore throat;	9/ 1/31	++++	++++	+++	+++	1.016	96	...	.....	0	112	80	Neg.	20	45	58
			tonsillitis	10/24/31	0	0	0	0	1.020	39	...	.....	..	120	80		48	15	22
24	14	M	Sore throat;	10/ 3/33	++++	++++	+++	++++	1.018	43	1.5	162.3	++	190	120	Convul-	24	38	70
			tonsillitis	12/15/33	0	+	+	0	1.024	30	1.4	183.2	0	126	70	sion	69	12	25
25	10	M	Tonsillitis;	11/14/33	++++	++++	++++	+	1.013	54	3.0	138.0	+	160	120	Neg.	12	9	25
			sore throat	2/18/34	0	0	0	0	1.018	30	1.8	151.5	0	110	70		52	8	18
26	33	F	Sore throat;	9/13/32	++++	+++	+++	++	1.024	44	3.2	.....	0	200	130	Convul-	31	34	49
			tonsillitis	10/13/32	0	0	0	0	1.016	28	1.4	.....	0	135	90	sion	72	12	16
27	30	F	Toxemia of	3/ 2/31	+++	+++	++++	+++	1.016	56	2.8	290	++	180	115	Neg.	24	40	55
			pregnancy	7/ 1/31	Trace	++	++	0	1.020	34	2.1	184	0	120	90		68	8	15
28	7	M	Common cold;	12/12/31	+++	++	+++	++	1.018	44	...	...	+++	130	80	Neg.	45	24	34
			influenza	3/10/32	0	0	0	0	1.020	33	...	...	0	98	60		105	18	32
29	16	M	Tonsillitis;	1/15/33	++++	+++	++	+++	1.013	40	2.2	...	+++	150	105	Neg.	29	28	58
			sore throat	11/21/33	+	0	++	0	1.021	35	2.6	...	0	120	80		56	9	16
30	17	F	Tonsillitis	5/11/32	+++	+++	+++	++++	1.017	67	...	...	+	150	100	Neg.	17	40	68
				7/15/32	0	0	0	0	1.024	43	...	...	0	122	70		55	10	21

CASE 6.—A white schoolgirl, aged 13, was first observed on July 13, 1931, following an attack of tonsillitis three weeks previously. There was slight edema about the eyes, and urinalysis showed: albumin 4 plus, many red blood cells and pus cells and a few granular casts. The blood pressure was normal, as well as the blood nonprotein nitrogen level and the reaction to the phenolsulphonphthalein tests. A blood urea clearance test was done repeatedly and gave values ranging from 65 to 75 per cent of normal. The erythrocyte sedimentation rate was 52 mm. during the first hour and 82 mm. during the second. After three weeks in the hospital the patient felt well and appeared to have made a complete recovery. A trace of albumin was found in the urine, with an occasional red blood cell and a few pus cells, but no casts. The blood pressure was normal; reactions to the tests of renal function were normal; the blood urea clearance was 70 per cent of normal. From the clinical as well as the laboratory standpoint she was making splendid recovery, and seemed to be progressing toward a healed stage. Had it not been for the rapid erythrocyte sedimentation rate of 54 mm. during the first hour, we should have considered her quite well. During the next several months she seemed very well, and all tests pointed toward recovery with the exception of the rapid sedimentation rate. On Nov. 6, 1932, edema reappeared, albuminuria became greater and the blood urea clearance test began to show a reduction in clearance for the first time. Although high blood pressure did not develop, the other syndromes of chronic glomerular nephritis gradually set in.

It is important, we believe, to stress that in dealing with cases in the transitional stage, the percentage of blood urea clearance may occasionally rise to normal figures, only to drop to below normal on subsequent tests. The opposite, too, may occur; an initial normal clearance may be followed by very low clearance, and subsequently there is a rise to normal, which level is maintained. An occasional estimation of the urea clearance, then, may lead one to false conclusions. Repetition, however, at regular intervals, over a period of several months, will show that in the healing stage clearances indicate a tendency to rise toward normal, while in those becoming chronic the tendency is toward a fall to decidedly low percentages.

Although the sedimentation rate of the erythrocytes has proved to be of value as an aid in the diagnosis and prognosis of many diseases, its use in nephritis has been sharply limited. As pointed out by Cutler,[17] the test is not specific and is not a procedure for diagnosing any particular disease, but is to be used rather as a general symptom, like fever and leukocytosis, is used. First, it serves to indicate the presence of some disease in the body which is causing the breakdown of tissue, and, second, the test is a measure of the intensity of the disease process. As a diagnostic aid in nephritis we believe it is an unessential test, but as a prognostic guide, indicating the degree of activity present in the kidney, it has been of considerable value. In following the patient with acute nephritis through the transitional stage it has proved to be of

17. Cutler, A. W.: The Practical Application of the Blood Sedimentation Test in General Medicine, Am. J. M. Sc. **183**:643, 1932.

distinct aid in showing whether the renal lesion was going on toward healing or to chronicity. This is not an infallible guide in the stage of transition, for we have had patients with genuinely active acute glomerular nephritis in whom the sedimentation rate has been normal. In conjunction with the other tests it is a valuable aid.

The theoretical explanation of this phenomenon is at present not clearly understood. Most authors have expressed the belief that an increased agglutinability of the erythrocytes plays an important rôle, and that the suspension stability of the red blood cells is influenced by the fibrinogen and globulin content of the blood. Whenever the fibrinogen and globulin contents are increased, the sedimentation rate of the red blood cells becomes more rapid. The rapidity of the sedimentation is in direct proportion to the degree and extent of the destruction of tissue, or the progress of certain pathologic conditions. Kylin [9] pointed

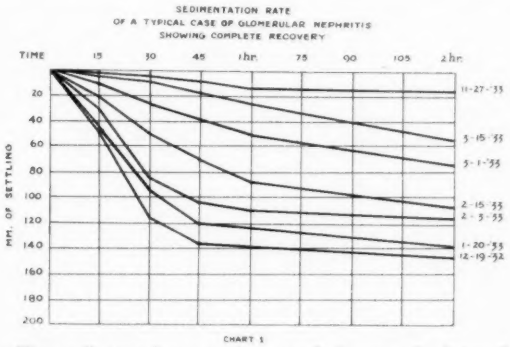

Chart 1.—The sedimentation rate in a typical case of glomerular nephritis showing complete recovery.

out that the changes in the plasma protein content play an important rôle in glomerular nephritis, producing an increased rate in the sedimentation of blood corpuscles, while in essential hypertension the stability of the plasma protein level is not affected and the sedimentation rate is normal.

We followed the original method of Westergren in studying the sedimentation rate of blood mixed with a 3.6 per cent solution of sodium citrate in a proportion of 1 part of sodium citrate to 4 parts of blood obtained by venipuncture. Into one of the special sedimentation pipets, which measures exactly 200 mm. from the zero mark to the tip, 1 cc. of citrated blood was taken up. The sedimentation of the red blood cells was measured at intervals of fifteen, thirty, forty-five and sixty minutes and two hours. The readings were plotted on graphs in each case, so that the progress or retardation of the sedimentation rate could be easily observed and compared.

The variations observed in the sedimentation rate in three typical cases of acute nephritis are shown by the graphs in charts 1, 2 and 3. Chart 1 shows a typical example of a case progressing satisfactorily to recovery; chart 2, a case resulting in death, and chart 3, a typical case which became chronic. Our observations with this test have led us to look on it as a fairly reliable gage of the progress of the renal lesion

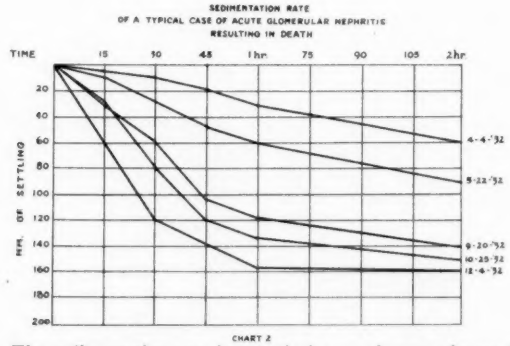

Chart 2.—The sedimentation rate in a typical case of acute glomerular nephritis resulting in death.

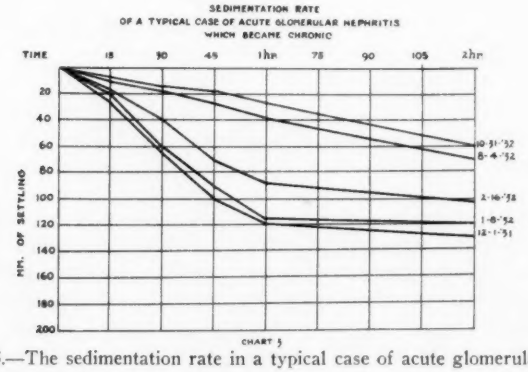

Chart 3.—The sedimentation rate in a typical case of acute glomerular nephritis which became chronic.

in the transitional stage. Our conclusions regarding the test may be given as follows: 1. In conjunction with the other tests enumerated, determination of the sedimentation rate is a valuable prognostic aid. 2. A single determination may lead to false impressions, and repeated tests may be necessary in order to arrive at a satisfactory decision. 3. A rapid rate is a warning signal that the renal lesion is active and progressing. 4. When the renal lesion is becoming quiescent the sedimentation

rate is less rapid; when the renal lesion is progressing the rate is more rapid. 5. The simplicity of the test is one of its best recommendations.

COMMENT

Acute nephritis is usually recognized when the attack is so severe that the renal function is for a time suppressed. This is followed by recovery, chronicity or death. Milder forms may pass unrecognized and untreated, and are frequently those which pass insidiously into the chronic form from which the patient rarely recovers. It is important to realize that the severest case of acute glomerular nephritis may heal promptly with no residual renal changes, while the mildest form may pass into the chronic. There seems to be a tendency to treat severe cases seriously, and to consider the acute case cured when the main syndromes have subsided. Owing to the fact that the immediate mortality in acute nephritis is low, many are led to view lightly the milder cases of acute nephritis and to be satisfied when the main symptoms of the acute stage have passed. We wish to emphasize that a mild infection of the type usually not considered important in the production of nephritis may be followed by an attack of acute diffuse nephritis so mild as to escape notice, and the signs and symptoms of this attack appear above the threshold of clinical recognition only after months or years have elapsed and the chronic stage has developed.

There is a pronounced lack of uniformity in the statistical reports of various authors concerning the etiology of acute diffuse glomerular nephritis. The disparity between the figures may be accounted for by the fact that some are compiled in hospitals for contagious diseases and others in children's hospitals, while still others are from general hospitals. If the urine were to be examined in all acute infections, both mild and severe, with the same care that it is examined in cases of scarlet fever, early and obscure cases of acute diffuse glomerular nephritis would more frequently be uncovered. As pointed out by Christian,[18] the prevention of nephritis is extremely unsatisfactory, and all that can be done is to prevent as far as possible and treat as thoroughly as possible all acute infections; closely allied, he added, is the prophylaxis of the common cold and its sequelae. We have become more and more convinced, as we have advanced in this clinical study, that the neglected acute infection of the upper respiratory tract is an important cause of acute nephritis and that the mild acute case later becomes the average chronic case with no history of previous scarlet fever or of an acute phase.

If such poorly defined cases are to be diagnosed and treated in their incipiency, then the usual textbook description of acute nephritis must

18. Christian, H. A.: Types of Nephritis and Their Management, J. A. M. A. **102**:169 (Jan. 20) 1934.

be set aside to a large degree. That hypertension, hematuria and edema are the important features of acute glomerular nephritis is, of course, true; but this triad develops only in the patient who has suffered such a severe attack that for a time the kidneys are overwhelmed. In some well developed cases all the syndromes do not appear at the same time. Occasionally, the hypertension remains for a day and disappears, and edema may be so slight as to pass undetected; and hematuria may be present in the beginning and last for a few days, then disappear, or it may never occur at all.

Scarlet fever can no longer be looked on as the chief cause of glomerular nephritis, and the main clinical features cannot be embraced under hematuria, edema and hypertension, as was done formerly. When it is taken into consideration that ordinary colds in the head may be a cause of acute nephritis, and that symptoms may pass unrecognized during the entire course of the disease, many more cases of the acute phase will be diagnosed when sought for. It is apparent that the common cold is a term which has been applied to a variety of types of infections of the respiratory tract. A clear definition of the common cold is difficult to obtain, because various investigators hold different ideas concerning its essential nature. We have used the term in the sense in which it is used by the Thomsons [19] in their monograph, "The Common Cold," in which they stated that the common cold is a generic term which covers a host of specific catarrhal infections of the mucous membrane of the respiratory tract. Concerning the term influenza, we found difficulty in differentiating between it and the common cold. The two terms are often used interchangeably, especially in periods during which no influenzal epidemic is present. In this series of cases the diagnosis of influenza was made when severe pains in the back and joints, headache and prostration dominated the clinical picture, and when the symptoms showed a tendency to be refractory to ordinary remedies. As pointed out by the Thomsons, although influenza and the common cold are very different diseases, the differential diagnosis is difficult, and no certainty in diagnosis will be forthcoming until definite causal organisms can be isolated with ease or until some scientific test has been developed. In grouping together these two etiologic factors in nephritis, we believe that we have avoided making a clinical separation in many cases, in which one practically does not exist.

Osman [20] said that it is wrong to consider scarlet fever as the most important cause of acute nephritis. He found that of fifty-six cases

19. Thomson, David, and Thomson, Robert: The Common Cold, Ann. Pickett-Thomson Research Lab. **8**:1 (Dec.) 1932.

20. Osman, A. A.: Etiology and Prognosis of Acute Nephritis in Children and Young Adults: Clinical Study of 56 Cases, Guy's Hosp. Rep. **75**:306 (July) 1925.

of nephritis thirty-three, or 59 per cent, followed infections of the upper respiratory tract, three developed during pneumonia, two followed the puerperium, three developed after exposure to chills and fever, and in fifteen cases no reliable cause could be obtained. He also showed from the investigation of two hundred and thirty-five cases that scarlet fever had occurred in only eight. Scarlet fever was responsible in only four cases of thirty-four reported by Guild.[21] Infections of the upper respiratory tract, such as the common cold and acute bronchitis, are the main causes in our experience. Other observers, including Boyd,[22] Rake,[23] Lichtwitz,[24] Hill [25] and Longcope and his associates,[2] found that infections of the throat and upper respiratory passages far outstrip scarlet fever as a cause of acute nephritis. Fishberg,[10] however, stated that scarlet fever is the most frequent cause of acute glomerular nephritis in children.

Evidence has been accumulating during recent years which tends to show that acute nephritis is one of the manifestations of late toxemia of pregnancy. Such an opinion has been expressed by Mussey and Keith,[5] who reported that in forty-two cases of acute toxemia, clinical evidence of nephritis was present in all but five. Similarly, in a series of five hundred and forty-five consecutive deliveries of patients with toxemia excluding eclampsia and vomiting, Peckham and Stout [26] found that reexamination of 66.6 per cent of these months later revealed definite chronic nephritis in 40 per cent of those examined. In eclampsia, a characteristic glomerular lesion was described by Bell.[6] An increase in the thickness of the capillary basement membrane and an increase of endothelial cells characterized the lesions. He concluded that the disease is a form of glomerular nephritis, but that it lacks some of the more striking features of acute glomerular nephritis; for instance, no epithelial crescents and no very large glomeruli are found. More recently, Baird and Dunn [7] studied the renal lesions in eclampsia and nephritis of pregnancy, and stated that the renal lesion closely simulates that of glomerulitis. In nine of ten cases of eclampsia they found the constant and predominant lesion to be in the glomeruli and to resemble that of acute glomerular nephritis.

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21. Guild, H. G.: Prognosis of Acute Glomerular Nephritis in Childhood, Bull. Johns Hopkins Hosp. **48**:193 (April) 1931.

22. Boyd, Gladys L.: Acute Nephritis in Children, Canad. M. A. J. **17**:894 (Aug.) 1927.

23. Rake, G. W.: The Rôle of Infections in the Etiology of Bright's Disease, Guy's Hosp. Gaz. **42**:242 (June 2) 1928.

24. Lichtwitz, L.: Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1925.

25. Hill, L. C.: Febrile Albuminuria, with Special Reference to Pneumonia, Quart. J. Med. **22**:305 (Jan.) 1929.

26. Peckham, C. H., and Stout, M. L.: Study of Late Effects of Toxemia of Pregnancy (Excluding Vomiting and Eclampsia), Bull. Johns Hopkins Hosp. **49**:225 (Oct.) 1931.

Although albuminuria is present in the urine of many patients with pneumonia, acute nephritis has been considered a rarity. Hill,[25] who studied albuminuria of pneumonia rather fully, stated that of twenty-one cases of pneumonia of all types, five, or 23.8 per cent, were accompanied by evidence of renal disease sufficient to justify a diagnosis of nephritis. Blackman and Rake [27] reported that acute glomerular nephritis was found in 9.4 per cent of ninety-five cases of pneumococcic infections; however, no instance of acute glomerular nephritis was found in thirty-two cases of lobar pneumonia. In our series, eight cases, or 8.5 per cent, were traced to pneumonia. At times it is difficult to decide whether the urinary changes signify only febrile albuminuria or genuine but mild glomerular nephritis. In some cases, other evidence of nephritis, such as hypertension, may help make the decision, but as a rule we decided the question on the urinalyses. If red blood cells and granular casts were present in addition to the albuminuria, and these persisted for a week or more after the pneumonic process subsided, we diagnosed the case acute glomerular nephritis. The diagnosis in many cases must rest on the urinalysis, for other symptoms, as edema, hypertension and retention of nitrogen, are often lacking. Persistent albuminuria, with red blood cells, granular casts and pus cells, after the subsidence of an infection or disease capable of producing renal inflammation is taken for evidence of acute nephritis. More accurate studies of the urine by the quantitative method of Addis [28] are doubtless of great value in the diagnosis of the acute lesion, as well as in determining whether the lesion is becoming chronic or is healing. Our experience with this method has been too limited for discussion, but we believe from what we have done that it is a definite aid in prognosis.

Differences of opinion prevail concerning the incidence of hypertension during the acute stage. Christian and O'Hare [29] stated that of fifty-five cases, hypertension developed in nineteen. According to Bennett,[30] a moderate degree of hypertension is found in a small proportion of cases, and cases with a greater degree of hypertension are those in which chronic nephritis preexisted. Lichtwitz,[24] Volhard,[1] Volhard and Fahr [31] and Kylin [9] believed that hypertension is always

27. Blackman, S. S., and Rake, G. W.: Acute Pneumococcal Nephritis, Bull. Johns Hopkins Hosp. **51**:217, 1932.

28. Addis, T.: Haemorrhagic Bright's Disease: Natural History, Bull. Johns Hopkins Hosp. **49**:203 (Oct.) 1931.

29. Christian, H. A., and O'Hare, J. P.: Nephritis, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1920-1921, vol. 3, p. 674.

30. Bennett, T. I.: Nephritis, Its Problems and Treatment, New York, Oxford University Press, 1929.

31. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

present during the acute stage. Others, as Fishberg [10] and Bennett,[30] expressed the belief that hypertension is more variable in its occurrence and apt to be absent at times. Our experience coincides with that of the latter group. One of our patients had no hypertension at the onset or during the course of the attack, and at autopsy typical acute diffuse glomerular nephritis was present. It is to be kept in mind, however, that hypertension may come and disappear in the early period of the acute phase before the reading of the blood pressure has been taken; furthermore, it may be absent at first and rise a few days later in the course of the disease. Kylin [9] stated that, as a rule, an increase of blood pressure comes first, and that changes in the urine develop some days later. He cited a case in which high blood pressure, edema and uremia occurred in the absence of the urinary syndrome. In our series we found the urinary syndrome present in all cases, and no other syndrome was found to develop earlier than this.

It has been customary to think of uremia as the chief cause of the fatal issue in cases of acute nephritis. Levy,[11] however, called attention to the circulatory disturbances found in ten patients with acute diffuse glomerular nephritis. He believed that hypertension is the cause of the cardiac insufficiency. It is undoubtedly true that hypertension plays an important part in causing heart failure in many cases, but that other factors, such as the toxic action of uremia alone, may be the causative agent in some cases, as has been shown by the report of our case A.

The edema of acute nephritis is such a striking feature of many cases that formerly some writers spoke of certain cases of acute nephritis with edema as if this were a distinct type of nephritis. Furthermore, some believed that edema often is the first sign of acute nephritis; but in many instances it is only the first sign noticed, as the changes in the urine precede the formation of edema. Edema may be so slight as to pass unnoticed or it may last for only a few days and disappear entirely or again it may return at a later date during the transition into the chronic stage. When edema occurs, there may be a mere puffiness of the eyelids; occasionally it is more widespread, but general anasarca is rare. In view of the fact that the presence of capillary damage has been cited as a cause of edema in acute nephritis and that such damage has not been proved, Rennie [32] attempted to determine whether any relationship exists between the degree of edema and the serum protein level in these cases. Of sixty-three cases in his series, nine, or 14 per cent, had low serum protein levels (below the edema-producing level). In these cases edema occurred, and he attributed it to a decrease in plasma protein. In other cases, the plasma protein levels were only slightly reduced, and edema also occurred. Rennie believed that in the latter a rise in the blood pressure plus the drop

32. Rennie, J. B.: Oedema in Nephritis, Quart. J. Med. **2**:521 (Oct.) 1933.

in the plasma protein level are jointly accountable for the edema. In a few cases in which no reduction of plasma protein was present a sharp rise in the blood pressure was, in Rennie's opinion, the main factor in causing the edema. Peters and Van Slyke [33] said that throughout the acute attack the plasma protein level may be unaffected, provided the attack is mild; otherwise there may be a decided fall in the protein level within a month. It must be taken into consideration, however, that in the earliest stages of acute nephritis, edema may dominate the clinical picture before any change occurs in the plasma protein osmotic pressure. They attributed this early edema not to a loss of protein osmotic pressure in the plasma, but to some quite different physical cause, presumably an increase in capillary permeability.

In our experience with this problem we have found slight or no reduction in the quality of plasma protein in the initial stage of the acute attack, when edema usually occurs. In the cases becoming subacute and chronic there was a tendency for the plasma protein level to fall. This reduction was pronounced in only a few cases and never as severe as that seen in lipoid nephrosis and chronic nephritis. In the cases which went on to the chronic stage, a fall in the plasma protein level was more commonly observed, and the determination of this decrease is one of the reliable prognostic guides. When edema developed during the latter periods of the acute stage in the patient whose condition went on to a chronic phase, a fall in the plasma protein to the edema-forming level was occasionally seen.

The term acute focal nonembolic glomerular nephritis is used by some, in contrast to acute diffuse glomerular nephritis, to designate cases characterized chiefly by albuminuria and the predominance of red blood cells in the urine. The absence of other features, like edema, hypertension and retention of nitrogen, is essential for this diagnosis. We believe that the clinical differentiation between genuine acute diffuse glomerular nephritis and the acute nonembolic focal type is difficult to make. We have seen the necessary symptoms on which to base a diagnosis of focal nephritis in cases which proved later to be genuine diffuse glomerular nephritis. Some observers look on cases of mild acute nephritis as a form of the focal type. Such mistakes in diagnosis frequently result in the lack of proper safeguards for the patient, whose ultimate fate is renal failure from a slow but progressive form of diffuse glomerular nephritis. Our observations have led us to believe that it is better to avoid making this clinical distinction in many cases in which practically none exists and to consider them as representative of a stage of diffuse nephritis rather than a distinct type.

33. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932.

With reference to the sedimentation rate of erythrocytes as a prognostic guide in nephritis, Kollert [34] found it of some help in determining whether or not the lesion of chronic glomerular nephritis was active or healing. In a critical analysis of the sedimentation test in its application to gynecology and obstetrics, surgery and general medicine, Walton [35] found that its most important use was that of a prognostic agent. In dealing with acute nephritis his case 143 was of particular interest to us. The patient was admitted to the hospital suffering from an attack of acute nephritis incidental to acute tonsillitis. A rapid sedimentation rate was found, but a month later, when all fever had subsided and albuminuria had ceased, another sedimentation test revealed a normal figure. In this case the nephritis cleared up promptly; if it had not cleared up, the sedimentation test perhaps would have remained rapid. The rapid sedimentation rates in many of our cases of acute nephritis were independent of the febrile stage of the causal disorder.

It is supposed by some, as pointed out by Aldrich and Boyle,[36] that there are cases of chronic glomerular nephritis which develop slowly and insidiously without having the initial acute stage. Perhaps a certain portion of such cases were in the unrecognized class during the mild acute onset, and passed unobserved into the chronic form. Such cases frequently illustrate that mild acute glomerular nephritis may develop and pass unrecognized through the transitional stage into the chronic form in a person who is oblivious of the fact that anything abnormal has occurred in the kidneys. We are aware that there is no measuring rod with which to determine accurately the degree and extent of the activity of the nephritic lesion in the stage of transition or in the early chronic phase. But if the simple methods outlined here are employed, it is possible that a better understanding of the true course of the disease may be obtained, resulting in an effort to prevent the onset of chronic glomerular nephritis by providing for the patient the proper safeguards which are often neglected.

SUMMARY

1. In ninety-four cases of acute diffuse glomerular nephritis the clinical features have been described, and essential data have been summarized in tables. Detailed information is given in tables 7 and 8 of twenty cases which became chronic and of ten selected cases in which recovery was made. The age incidence in relation to outcome, the

34. Kollert, V.: Nephritis, Aerztl. Praxis **6**:1 (Jan. 15) 1932.

35. Walton, A. C. R.: The Erythrocyte Sedimentation Test, A Clinical and Experimental Study, Quart. J. Med. **2**:79 (Jan.) 1933.

36. Aldrich, C. A., and Boyle, H. H.: Chronic Nonspecific Nephritis: Clinical Observations on 40 Children with Results of Treatment on Full Diets, J. A. M. A. **100**:1979 (June 24) 1933.

causes of death in twenty-seven cases, the etiologic agents and the chief clinical syndromes have been analyzed clinically.

2. Acute diffuse glomerular nephritis may result from mild forms of infection of the upper respiratory tract, not usually considered as causal factors in acute nephritis.

3. The acute phase of glomerular nephritis may be so mild that it passes unrecognized, and no indication of renal damage is observed until the disease has progressed into the chronic stage, when renal insufficiency sets in.

4. There is a period in the course of the disease, coming after the early symptoms of the acute phase have subsided, that is called the stage of transition, in which the patient is frequently considered cured; but in reality the renal lesion continues to be unhealed, and progresses toward the chronic stage unrecognized and untreated.

5. It has been shown that if the cases in this period are studied with the aid of the several simple methods given here, the true course of the disease may be determined. Special attention has been paid to the blood urea clearance test and the erythrocyte sedimentation rate in determining whether the renal lesion has completely healed or has become quiescent temporarily, only to become active later on.

6. A study of cases in the stage of transition is of utmost importance, because if the true condition is recognized at this time the proper safeguards may be provided which perhaps will interrupt the progress of the renal inflammation before chronic glomerular nephritis has come to full fruition.

EFFECT OF CARDIAC INFARCTION ON THE TOLERANCE OF DOGS TO DIGITALIS

AN EXPERIMENTAL STUDY

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The literature concerning the tolerance to digitalis in clinical cases of coronary occlusion is meager. The few reports with which we are acquainted consist chiefly of clinical impressions. Moreover, the conclusions of various observers are not entirely in agreement. Herrick [1] stressed the great value of digitalis in coronary occlusion and suggested that rapid effects be sought in some cases by intravenous or intramuscular injection. Riesman [2] felt that digitalis should not be used in coronary occlusion, believing that because of its great damage to the myocardium it would do no good and might do harm. Bastedo [3] stated that in cases of coronary sclerosis and myocarditis, regardless of rhythm, digitalis must be used with care and never in massive doses.

Conclusions based on experiments with animals likewise are somewhat at variance. Gold [4] reported in 1925 that there was no significant variation in the tolerance of cats to ouabain after coronary occlusion as compared to those in a control group. He concluded that "the experimental evidence lends no support to the fear that in coronary occlusion digitalis may precipitate ventricular fibrillation more readily than in the normal heart." Gilbert and Fenn [5] obtained a decrease in the coronary flow in dogs treated with digitalis which they believed was due to vaso-

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1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **69**:2015 (June 22) 1912.

2. Riesman, D.: Coronary Thrombosis, M. Clin. North America **6**:851, 1923.

3. Bastedo, W. A.: The Present Status of Digitalis Therapy, Ann. Clin. Med. **5**:993, 1927.

4. Gold, H.: Action of Digitalis in the Presence of Coronary Obstruction, Arch. Int. Med. **35**:482 (April) 1925.

5. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**:668 (Nov.) 1932.

constriction. They stated that a great deal of caution should be used in the administration of digitalis in the presence of coronary disease.

Because of the widespread tendency to use digitalis in the presence of any severe cardiac weakness, tolerance of the recently infarcted heart to digitalis and the wisdom of using this drug in large doses under these conditions would seem to be important.

Since the matter is a difficult one to settle by clinical observation alone, we attempted to study the matter further by experiments, realizing at the same time the limitations that stand in the way of applying such results directly to human medicine.

METHOD

Dogs weighing from 7.6 to 15.0 Kg. were used for our experiments. The anterior descending branch of the left coronary artery and, in some cases, the accompanying vein were ligated in continuity, as described in a previous report,[6] in order to produce occlusion and subsequent infarction. After varying periods of time (from thirty minutes to six months) the tolerance of the animal to digitalis was determined by a method similar to that described by Burn[7] for the assay of digitalis on cats. Freshly prepared tincture of digitalis diluted twenty times with physiologic solution of sodium chloride was given by continuous infusion into the femoral vein at a rate of 0.025 cc. per kilogram of body weight per minute. By using a tincture of about standard strength, this rate of administration was sufficient to cause death in normal dogs in from thirty to forty-five minutes. Light ether anesthesia and artificial respiration were used on all animals except in four of the control experiments on normal animals. Blood pressure of the carotid was recorded graphically during administration of the drug. At the conclusion of the experiment the heart was carefully removed and examined for pathologic changes. Usually an area of infarction involving the apex, anterior wall and a portion of the lateral wall of the left ventricle was seen.

RESULTS

Table 1 shows the results obtained in the assay of the tincture on normal dogs. Two tinctures varying slightly in strength were used. With tincture A, the lethal dose ranged from 0.8 to 0.94 cc. per kilogram in four experiments in which artificial respiration was not used, the average being 0.85 cc. per kilogram. In two dogs on which artificial respiration was used the average lethal dose was 0.90 cc. per kilogram. With tincture B, the lethal dose varied from 0.84 to 1.16 in seven dogs and averaged 1.02 cc. per kilogram. Artificial respiration was used on all these animals. From these data it was concluded that the lethal dose in dogs by the method used gave figures which varied

6. Bellet, S., and Johnston, C. G.: The Effect of Coronary Occlusion Upon the Initial Phase of the Ventricular Complex in Direct Chest Leads: An Experimental Study, J. Clin. Investigation **13**:725, 1934.

7. Burn, J. H.: Method of Biologic Assay, New York, Oxford University Press, 1928.

within a fairly small range.[8] The values obtained from the lethal dose were apparently slightly higher when artificial respiration was used. In some of the dogs under artificial respiration a sudden drop in pressure almost to zero was noted from two to three minutes before death. This pressure gradually rose again and continued for a brief period before finally dropping to zero. This preagonal drop might have been considered the end-point in these dogs if artificial respiration had not been used.

TABLE 1.—*Standardization of Normal Dogs*

Date of Standardization	Dog	Weight, Kg.	Tincture A Lethal Dose, Cc. per Kg.	Tincture B Lethal Dose, Cc. per Kg.	Time of Infusion, Min.
4/13/33	878	13.8	0.80	....	33.0
4/13/33	881	12.8	0.94	....	38.0
4/18/33	885	12.7	0.82	....	33.5
4/20/33	892	12.0	0.85	....	34.0
5/30/33	1,025	15.0	0.92	....	37.0
5/30/33	1,029	12.5	0.88	....	35.5
6/20/33	1,043	13.3	....	1.13	46.0
6/20/33	1,024	12.0	....	1.15	45.0
7/ 8/33	6	11.9	....	1.16	46.0
7/ 8/33	7	14.0	....	0.94	37.5
7/13/33	8	15.8	....	0.86	34.5
7/13/33	9	11.2	....	0.84	33.5
7/13/33	10	13.9	....	1.05	42.0

TABLE 2.—*Standardization Four Days After Operation; No Infarction Present (Control Animals)*

Date of Standardization	Dog	Weight, Kg.	Tincture A Lethal Dose, Cc. per Kg.	Tincture B Lethal Dose, Cc. per Kg.	Time of Infusion, Min.
4/27/33	891	7.8	0.85	....	33.0
5/ 6/33	910	9.0	0.89	....	37.0
5/ 6/33	911	7.6	0.85	....	34.0
6/18/33	960	7.9	....	1.28	51.5

Table 2 shows the values obtained in the animals to which digitalis was administered four days after operation without coronary occlusion. They were subjected to the same operative procedure as the animals in which cardiac infarction was produced except that the coronary artery was not tied. They therefore served as excellent controls in our study of the effect of the operative procedure on the tolerance to digitalis. The values obtained with tincture A ranged from 0.85 to 0.89 cc. per kilogram. With tincture B the value was 1.28 cc. per kilogram in one dog. These values were practically identical with the normal values obtained for these animals with the respective tinctures, and they indi-

8. Ten dogs were standardized with a third tincture for another type of experiment. The lethal dose varied from 0.96 to 1.15 cc. per kilogram, the maximum variation being about 10 per cent above or below the average. By the method used, the figures for standardization in the dog varied within a much narrower range than those in the cats.

cated that the operative procedure per se had no effect on the tolerance of the animals to digitalis four days after operation.

Table 3 shows the figures obtained in the experiments in which the tolerance was determined from thirty to forty minutes after ligation of the coronary artery. In three of these dogs the values ranged from 0.85 to 0.89 cc. per kilogram, practically the same as those obtained in the normal animals. In the remaining two of the five animals the values were even slightly higher than those obtained in normal animals. The probable cause and significance of the latter values will be discussed later. It may be said, however, that there was no evidence of a decrease

TABLE 3.—*Standardization One-Half Hour After Ligation of Anterior Descending Branch of Left Coronary Artery and Vein*

Date of Standardization	Dog	Weight, Kg.	Tincture A Lethal Dose, Cc. per Kg.	Time of Infusion, Min.
4/29/33	903	12.0	0.85	54.0
4/29/33	904	14.8	0.89	38.0
5/ 2/33	912	13.0	0.89	35.5
4/22/33	894	12.0	1.00	41.0
5/22/33	997	13.2	1.03	41.3

TABLE 4.—*Dogs Standardized Four Days After Coronary Ligation, All Showing Cardiac Infarction*

Date of Operation	Date of Standardization	Dog	Weight, Kg.	Tincture A Lethal Dose, Cc. per Kg.	Tincture B Lethal Dose, Cc. per Kg.	Time of Infusion, Min.	Comment
4/14/33	4/18/33	879	16.0	0.70	....	28.0	Large infarction
4/26/33	4/29/33	858	11.7	0.65	....	26.5	Large infarction
5/18/33	5/23/33	985	8.7	0.69	....	28.0	Large infarction
5/20/33	5/24/33	991	14.5	0.63	....	25.0	Very large infarction
6/14/33	6/18/33	993	7.8	....	0.77	31.0	Large infarction
6/19/33	6/23/33	932	15.0	....	0.77	31.0	Medium infarction
6/21/33	6/25/33	1,052	15.0	....	0.85	34.0	Small infarction

in tolerance in digitalis from thirty to forty minutes after ligation of the coronary arteries.

Table 4 shows the results obtained when digitalis was administered to dogs on the fourth day after ligation of the coronary artery. These dogs had definite infarction of the muscle of the heart which varied somewhat in extent in the different animals. With tincture A the values in four dogs ranged from 0.63 to 0.70 cc. per kilogram. With tincture B the figures for the lethal dose in three dogs were 0.77, 0.77 and 0.85 cc. per kilogram, respectively. The area of infarction in the last dog was quite small, its extent being less than that in any of the others of this group. The average lethal dose was 0.8 cc. per kilogram, as compared to 1.02 cc. in the normal dogs.

These figures were definitely below the range of values obtained in the normal dogs. Except for one animal (dog 1052) which received

tincture B and in which the infarction was small, the tolerance of the animals with the acute infarction was below even the lowest figures of the animals in the normal control groups. The decrease in tolerance ranged from about 20 to 30 per cent below the average for the normal controls. In spite of the presence of cardiac damage the animals appeared to be in fair condition before the final assay. In general, the dogs showing the largest infarction exhibited the poorest tolerance to digitalis.

Table 5 shows the values obtained in four dogs in which ligation of the coronary artery was performed from six weeks to six months before assay. These animals had infarctions involving the apex and the lower portion of the anterior wall of the left ventricle. During the chronic stage the extent of infarction was considerably less than in the acute stage. These animals were studied electrocardiographically during this period, and tracings taken in the latter part of this period

TABLE 5.—*Standardization in Chronic Infarction*

Date of Operation	Date of Standardization	Dog	Weight, Kg.	Lethal Dose Tincture A, Cc. per Kg.	Lethal Dose Tincture B, Cc. per Kg.	Time of Infusion, Min.
10/20/32	5/ 4/33	328	11.8	0.75	....	29.5
10/21/32	5/ 4/33	261	13.0	0.75	....	30.0
5/30/33	7/15/33	803	15.6	....	0.79	32.3
5/30/33	7/15/33	959	9.0	....	1.00	40.0

showed a considerable return to normal, indicating that healing had taken place. The lethal dose for these animals was 0.75 cc. per kilogram with tincture A. In two dogs standardized with tincture B six weeks after ligation of the coronary artery the lethal dose was 0.79 and 1 cc. per kilogram, respectively. Both animals showed an area of chronic infarction about 2 cm. in diameter involving the anterior wall of the left ventricle near the apex. In three of the four animals with chronic infarction the lethal dose was below that required for the normal, and the values obtained ranged approximately between those obtained for the animals with acute infarction and those for the normal controls. In one dog the lethal dose was within the normal range.

COMMENT

Choice of the experimental animal is not an unimportant matter. In our early experiments we used the cat, as did Gold [4] in somewhat comparable experiments. We discarded this animal for the dog for two reasons: First, the end-point in the cat, as determined by the fall in blood pressure to zero, was often gradual and not rapid. Second, cats

withstand ligation of the coronary artery quite well,[9] and are often resistant to the inception of ventricular fibrillation. We were able to ligate both coronary arteries in some of these animals without ventricular fibrillation occurring. Moreover, in the instances in which ligation of isolated coronary arteries produced ventricular fibrillation, this arrhythmia not infrequently reverted spontaneously to a normal rhythm. We never observed this in the dog, although rare instances of recovery from ventricular fibrillation under these conditions have been reported.[10]

There appears to be a sound physiologic reason why the heart of the cat is more refractory to the development of ventricular fibrillation than that of the dog. McWilliam [9a] noted that spontaneous recovery from ventricular fibrillation took place readily in the heart of the cat, rabbit, mouse, hedgehog and fowl in contrast to the hearts of larger animals. He found that the large beef heart, for example, entered into the fibrillary state with the greatest ease and caprice. Garrey [9b] demonstrated that the ease with which the fibrillary process may be induced, and with which spontaneous recovery from the fibrillary contractions takes place is, in general, inversely proportional to the mass of fibrillary tissue.

In view of these considerations, we discontinued the use of the cat in favor of the dog after a few preliminary experiments [11] because we felt that the effects of ligation of the coronary artery in the larger heart of the dog were more comparable to those observed in the human heart. Dogs proved quite satisfactory for these experiments. By the method used they were standardized with a fair degree of accuracy and the end-point, as denoted by a sudden drop in blood pressure in practically all cases, was definite and clearcut.

RELATIONSHIP BETWEEN THE STAGE OF INFARCTION AND THE TOLERANCE TO DIGITALIS

Ligation of a coronary artery sets off a series of events in the muscle involved that lasts for a variable period of time (from four to six weeks) until the chronic stage is reached. First, there are inaugurated the processes that lead to death and necrosis, which may not reach their maximum development for several days after coronary

9. (*a*) McWilliam, A.: Fibrillar Contraction of the Heart, J. Physiol. **8**:296, 1887. (*b*) Garrey, W. E.: The Nature of Fibrillary Contraction of the Heart: Its Relation to Tissue Mass and Form, Am. J. Physiol. **33**:397, 1914.

10. Porter, W. T.: The Recovery from Fibrillary Contractions, Am. J. Physiol. **1**:71, 1898.

11. In our initial experiments with cats no definite diminution in tolerance to digitalis was noted, even with definite myocardial infaction from six to eleven days after ligation of the coronary artery. In these instances the end-point was not clearcut, and the fall in blood pressure was gradual and was maintained over a relatively long period.

occlusion. These are followed by the slower processes of healing. At varying stages in this somewhat protracted process, the histologic condition of the muscle varies greatly.

In the chronic stage, for example, six weeks or more after ligation of the coronary artery, the muscle is demonstrably abnormal only to the extent of having a scar, all evidences of inflammation and necrosis having been removed. In contrast, in the acute or subacute stage, a few days after ligation, the involved myocardium shows inflammation, edema and necrosis, and the muscle is thick, boardlike and probably noncontractile.

In a still earlier stage, from a few minutes to one-half hour after ligation, in spite of the presence of currents of injury as revealed by the electrocardiograph, no histologic evidences of infarction are present. For some time after occlusion, the changes in the muscle are probably reversible; i. e., if circulation can be restored, the muscle will return to normal. We saw this occur in two dogs when a ligature, applied tightly enough to produce typical electrocardiographic effects, and known to have been effective for at least fifteen minutes, subsequently slipped and permitted the muscle to be entirely restored to normal, so far as histologic and electrocardiographic studies revealed.

Between this stage and that of maximum necrosis, the changes undergone by the muscle are great and more or less progressive. Just when the stage of maximum necrosis is reached we do not know, but we suspect that from twenty-four to forty-eight hours at least are required for its full development. We suspect this not only because of the histologic observations made on the hearts used in these experiments, but because of electrocardiographic studies of coronary occlusion in hearts of both dog and man. It is a common experience to find that the curves obtained by semi-direct leads of the chest do not reveal their maximum change for twenty-four hours, or even longer, after occlusion has taken place.[6]

Feeling that the tolerance to digitalis after coronary occlusion might be directly related to and depend on the degree of pathologic change in the involved muscle, we made our determinations during three stages of this complicated process: one-half hour after ligation, from three to four days after occlusion and in the period of from six weeks to six months after the original ligation.

As we have already pointed out, our results indicated a rather striking diminution of tolerance in the stage of maximum necrosis, a slightly diminished tolerance in the chronic or healed stage and a normal tolerance in the period of from thirty to forty minutes after closure of the coronary artery. Moreover, the degree of diminished tolerance noted during the stage of necrosis appeared to be proportional to the size of the necrotic area. That the operation itself had no effect on the tolerance to digitalis was shown by the results obtained in the animals

which had been subjected to exactly the same operative procedure as those with myocardial infarction, with the exception that the coronary arteries were not ligated. The tolerance of these animals to digitalis was within normal limits (table 3).

These results point to conclusions that are different from those drawn by Gold [4] from somewhat comparable experimental work. His method, however, differed from ours in two important respects. First, he used cats which, as we have already pointed out, appear to withstand ligation of the coronary artery particularly well. Second, his determinations of tolerance were made at a relatively early stage in the process of infarction, from forty minutes to twenty-four hours after ligation.

Because of physiologic reasons already cited, we feel that results obtained in dogs are more apt to be applicable to man than those obtained in smaller animals. Therefore, we believe that our conclusions have certain implications, at least in the human problem. We are more willing to give them weight in this connection because they coincide with our clinical impressions, which lean strongly to the view that the more damaged the heart is, the less is its tolerance to digitalis.

SUMMARY

The tolerance of dogs to digitalis was determined at various intervals of time after ligation of the coronary artery: one-half hour after ligation of the coronary artery; four days later (during the stage of acute and subacute infarction) and from six weeks to six months later (during the stage of chronic infarction). The tolerance of these animals was compared with that of animals in a normal control series.

Dogs standardized within one-half hour after ligation showed no diminution in tolerance to digitalis as compared with those in a control group. During the stage from acute to subacute infarction there was a diminished tolerance to digitalis which averaged from about 20 to 30 per cent below the average of the figures for the normal controls.

In the animals with chronic infarction, in which the area of infarction was considerably smaller than in the acute or subacute stage (standardized from six weeks to six months after ligation of the coronary artery), the tolerance was less than that of the normal animals but higher than that of the group with the subacute infarctions.

The diminution in tolerance after ligation of the coronary artery apparently depends on the presence of infarction and probably also on the extent and stage of the infarcted area. These findings lend support to the clinical impression that digitalis in massive doses may be dangerous during the stage of subacute and chronic infarction, and that it should be used with caution in such cases.

Dr. A. N. Richards placed the facilities of his laboratory at the disposal of the authors, and Dr. C. F. Schmidt furnished valuable advice.

RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND NITROGEN METABOLISM

IV. EXPERIMENTS ON ANIMALS

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Variations in the rate of oxygen consumption are met with in numerous conditions in which no disturbance in thyroid function has been recognized. Prominent among such conditions are the hematopoietic diseases. In a series of investigations I have attempted to evaluate some of the abnormal physiologic processes in the blood dyscrasias in terms of their effect on the oxidative processes of the organisms as a whole. Studies have been made on patients with pernicious anemia, leukemia and polycythemia vera, as well as on dogs with acute hemorrhagic anemia, hemolytic anemia, induced polycythemia and phlorhizin diabetes.

The previous communications concerning pernicious anemia, leukemia and polycythemia vera will be briefly summarized. The reader is referred to the original publications for details and bibliographies.

STUDIES ON MAN

Pernicious Anemia.—The object of the studies of pernicious anemia, which were carried out by my associates and me was to determine the effect of rapid erythropoiesis on the total oxygen consumption. Ten patients with severe pernicious anemia were studied, and part of the data have been published.[1] The pertinent information derived from these studies may be summarized as follows:

1. In eight of the ten patients the total oxygen consumption decreased during the period of most rapid erythropoiesis. In the other two patients there was no significant change in the gaseous metabolism. In the eight cases the total decrease in basal metabolic rate varied from 50 to 15 per cent. In patients who were without fever and for whom the control periods were sufficiently long the decrease was found to be between 15 and 20 per cent. This drop occurred regardless of whether the control level was above or below the calculated normal.

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1. Baldridge, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: I. In Pernicious Anemia, J. Clin. Investigation **10**:529, 1931.

2. During the period of rapid erythropoiesis and decreased oxygen consumption there was moderate storage of nitrogen in all of the four cases in which nitrogen balances were determined.

3. One large dose of liver extract per week by mouth caused the same gradual decrease in oxygen consumption which occurred with smaller daily doses.

4. In nearly every instance the total oxygen consumption gradually decreased throughout the reticulocytic crisis.

5. It is obvious that the formation of blood greatly exceeded the destruction of blood during the period of decreasing oxygen consumption.

Leukemia.—Chronic leukemia under treatment by irradiation affords a circumstance in which the destruction of blood temporarily exceeds the formation of blood. Nine patients with chronic leukemia were studied before and after irradiation, and the data have been published.[2] The reader is referred to this publication for details of the metabolic studies and for a discussion of the existing theories as to the cause of the increased gaseous metabolism in leukemia.

The results of our investigations on leukemic patients may be summarized as follows:

Following a large dose of roentgen irradiation there is an abrupt increase in the excretion of nitrogen. The nitrogen balance becomes negative, owing to decreased ingestion and increased endogenous nitrogen catabolism. The total oxygen consumption increases within six hours after irradiation, and the increase may last for four days or may disappear within twenty-four hours. The magnitude and duration of the increase in gaseous metabolism seem to depend on the degree and duration of protein catabolism occasioned by the irradiation.

After the preliminary increase in the excretion of nitrogen which follows irradiation, the urinary nitrogen gradually decreases, often to a level below that of the control period. During this period of lowered catabolism of protein the nitrogen balance becomes positive, and the gaseous metabolism decreases.

Polycythemia Vera.—In polycythemia vera, the destruction of blood can be made to exceed the formation of blood by the administration of phenylhydrazine. Two patients with polycythemia vera were studied during intoxication by phenylhydrazine, and the data have been reported.[3]

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2. Baldridge, C. W., and Barer, A.: Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia, Arch. Int. Med. **51**:589 (April) 1933.

3. Barer, A.; Paul, W. D., and Baldridge, C. W.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: III. In Polycythemia Vera, J. Clin. Investigation **13**:15 (Jan.) 1934.

The results of our studies of leukemia and polycythemia vera were quite similar so far as the relationship between nitrogen catabolism and oxygen consumption was concerned. Phenylhydrazine produced a marked decrease in the number of erythrocytes, a negative nitrogen balance, due largely to the increased catabolism of protein, and an increase in the basal metabolic rate. No attempt has as yet been made to establish a quantitative relationship between the loss of endogenous nitrogen and the increase in oxygen consumption by the body, but the destruction of nonnucleated erythrocytes by phenylhydrazine seems to require about as much oxygen per gram of nitrogen as does the destruction of nucleated leukemic cells by irradiation.

ADDITIONAL STUDIES ON ANIMALS

The oxygen consumption of the dogs was measured by the Benedict closed circuit apparatus with attachments described by Kunde.[4] Four well trained dogs were used. Before control periods were begun, tests were made daily for periods of ten, thirteen and twenty-eight days, respectively, on three previously trained dogs. Dog 4 had not previously been trained, so that a control period was not begun until the oxygen consumption was fairly constant and the average for several days was below the calculated normal consumption. Tests were made at about the same time each day, at least twenty hours after food was taken and after a preliminary period of rest of at least twenty minutes. The tests were run for twenty minutes, and calculations were based on the last fifteen minutes of this period. Determinations were made daily without exception over a period of about eight months. On a few occasions when extraneous influences of one kind or another caused the dogs to move, the tests were repeated. Seven times the second test was unsatisfactory, and though it was recorded, it was not used in the calculations of averages. Two other determinations were unsatisfactory because the dogs obtained food by mistake. Thus, of a total of eight hundred determinations, nine were considered to be unsatisfactory. One dog suffered a short febrile illness after bleeding, which invalidated the results of one experiment (dog 3, chart 4).

According to the work of Kunde and Steinhaus,[5] the average basal metabolism of normal dogs is 771.2 calories per square meter each twenty-four hours. This figure has been used as the normal, and the surface area has been calculated from Meeh's formula.[5] As no attempt has been made to compare the metabolism of one animal with that of another, there is no need to discuss the shortcomings of the Meeh formula for the determination of the surface area of the dog. All of the temperatures were taken rectally.

Hemorrhagic anemia was produced by bleeding the dogs with a needle from the jugular or femoral veins. About 25 cc. of blood per kilogram of body weight was removed on each of two successive days. The blood was removed just after the determination of the basal metabolic rate on the day indicated.

Transfusions were done by the indirect method, the blood being given by means of gravity. Fifty cubic centimeters of 2.5 per cent sodium citrate solution was used

4. Kunde, M. M.: The After Effects of Prolonged Fasting on the Basal Metabolic Rate, J. Metab. Research **3**:399, 1923.

5. Kunde, M. M., and Steinhaus, A. H.: Studies on Metabolism: IV. The Basal Metabolic Rate of Normal Dogs, Am. J. Physiol. **78**:127 (Sept.) 1926.

as an anticoagulant for each transfusion. About 50 cc. of whole blood per kilogram of body weight was given in experiments 5, 6 and 7. In experiment 8 *B*, dog 1 died the day after receiving 375 cc. of whole blood. The blood given in experiments 5, 6 and 7 was found to be compatible by cross-matching. The blood given to dog 1 in experiment 8 *B* was from the donor that had been used in the three transfusions for dog 1 in experiment 5, but cross-matching was not done before the last and fatal transfusion.

The citrated plasma which was given intravenously in experiments 8 *A* and 9 *B* was obtained from the donors from which these recipients had previously received transfusions of whole blood. In each instance the whole blood had been diluted with 50 cc. of 2.5 per cent sodium citrate, and the citrated plasma obtained by centrifugation.

In experiments 9 *A*, 10 *A* and *B* and 11 *A* the corpuscles and plasma were separated by centrifugation, and the corpuscles were hemolyzed by the addition of distilled water.

The charts for the experiments with phlorhizin are almost self-explanatory. One gram of phlorhizin was given in each instance. Merck's phlorhizin was recrystallized from alcohol as suggested by Lusk.[6] The recrystallized phlorhizin was dried and suspended in sterile olive oil for subcutaneous injection. The loss of nitrogen through the feces and hair was not determined in these animals.

The diets were as follows:

Dogs 1 and 2, from June 22 to July 13, 1931, were given 250 Gm. of chopped beef lung, 225 Gm. of bread, 250 cc. of milk and about 20 Gm. of bone meal daily in one feeding. From July 14 to October 9, 200 Gm. of chopped beef lung was given; the other constituents were unchanged. From October 10 until the death of dog 1 on December 2 and until the beginning of the phlorhizin experiment in dog 2 on December 17, the chopped beef lung was reduced to 150 Gm. daily, with no other change in the diet.

Dog 3 was given chopped beef lung as follows: from June 22 to July 13, 1931, 300 Gm. daily; from July 14 to October 9, 250 Gm. daily and from October 10 to Jan. 9, 1932, 200 Gm. daily. The amounts of bread (225 Gm.), milk (250 cc.) and bone meal (about 20 Gm.) remained constant from June 22, 1931, to Jan. 9, 1932.

Dog 4 was obtained on July 21, 1931; his diet corresponded with that of dogs 1 and 2 until the beginning of the experiment with phlorhizin on December 24.

Liver extract, when given, was given in addition to the regular diet. Liver extract with iron (equivalent to 300 Gm. of whole liver) was given daily for twenty days to each of the dogs that were bled. In dog 3 it was begun immediately after bleeding while in dogs 1 and 2 it was started ten days after bleeding.

Several determinations were made in addition to the metabolic studies. The weight, pulse rate, respiratory rate, temperature, hemoglobin (Sahli), hematocrit value and erythrocyte and leukocyte counts were determined daily. For these determinations 1 cc. of blood was withdrawn from a vein and added to a few small crystals of neutral potassium oxalate. Care was taken to prevent settling of the corpuscles.

RESULTS

Acute Hemorrhagic Anemia.—After control periods of twelve, twelve and fifteen days, respectively, dogs 1, 2 and 3 were bled about

6. Lusk, G.: The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1928, p. 626.

25 cc. per kilogram of body weight on each of two successive days (charts 1, 2, 3 and 4). The dogs had been in the laboratory for many months and had been on an adequate diet, so that the blood counts of the controls were higher than the average for recently impounded dogs. After bleeding there was a gradual restitution of hemoglobin and erythrocytes in each instance. The previous normal level was reached in about twenty days, while at the end of thirty days after bleeding

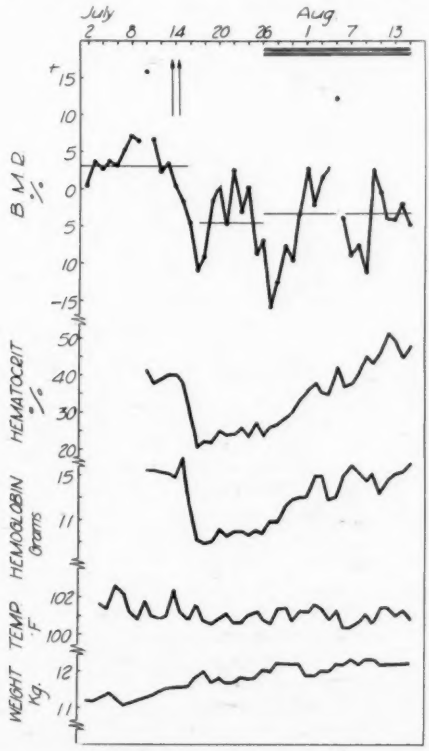

Chart 1 (dog 1).—Two hundred and seventy cubic centimeters of blood was drawn on July 13, and 270 cc. on July 14, 1931, as indicated by the arrows. The dog weighed 11.5 Kg., and the blood volume of all of the dogs was estimated to be 100 cc. per kilogram of body weight. The control period was twelve days, but on one day the metabolism test was unsatisfactory. Liver extract with iron (equivalent to 300 Gm. of whole liver per day) was given for twenty days beginning ten days after bleeding, as indicated by the parallel lines in the upper right hand corner. Here, as in all of the subsequent charts, the control average and the averages for ten-day periods during the experiment are indicated by horizontal lines through the curve of the basal metabolic rate.

there was a distinct and permanent overcorrection in the hemoglobin and the number of erythrocytes. During the first ten days of this period of rapid formation of blood the average oxygen consumption was found to be 7.1, 7.9 and 9.3 per cent, respectively, below the control averages. The basal metabolic rates continued low throughout the entire period of blood regeneration, during which all of the dogs gained in weight (0.4, 1 and 1.2 Kg., respectively). Nitrogen balances were not deter-

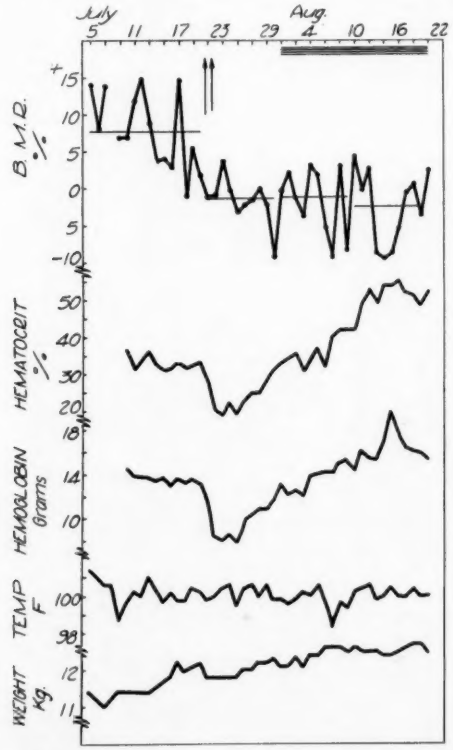

Chart 2 (dog 2).—Two hundred and seventy cubic centimeters of blood was drawn on July 20, and 285 cc. on July 21, 1931. Liver extract was given as in the previous instance (dog 1).

mined, but it is assumed for obvious reasons that the animals were storing nitrogen as well as carbon during the period of recovery.

Dog 3 was bled again at a later date, but an acute febrile illness with vomiting, anorexia and loss of weight followed immediately after the bleeding, so that the results of the experiment were completely invalidated.

The literature on the subject under consideration, though not extensive, is in direct contrast to these results. Eberstadt [7] found that the gaseous metabolism in rabbits with hemorrhagic anemia was increased, and Rolly [8] reported a similar rise in the oxygen consumption of dogs after bleeding. Logical objections to the work of these investigators

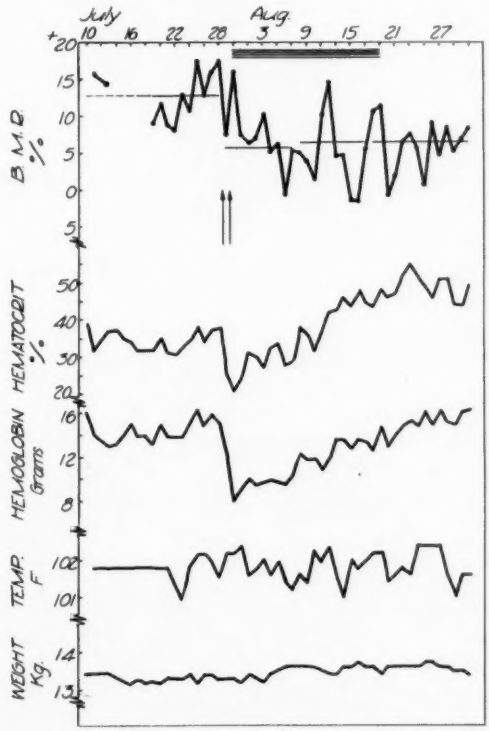

Chart 3 (dog 3).—Three hundred and twenty-five cubic centimeters of blood was drawn on July 28, and 280 cc. on July 29, 1931. Liver extract was given for twenty days, starting immediately after bleeding.

can be based on the fact that determinations on controls were few and on the fact that there was no evidence that the animals had been

7. Eberstadt, F.: Ueber den Einfluss chronischer experimenteller Anämien auf den respiratorischen Gaswechsel, Arch. f. exper. Path. u. Pharmakol. **71**:329, 1913.

8. Rolly, F.: Ueber den respiratorischen Gaswechsel bei chronisch anämischen Zuständen, Deutsches Arch. f. klin. Med. **114**:605, 1914.

trained. Hawk and Gies [9] found a negative nitrogen balance in dogs after severe hemorrhage. However, the blood was let under ether anesthesia, and the arteries were cannulated and tied off after the blood was obtained. The femoral artery or some of its branches were used and were permanently occluded. Some slight increase in the urinary

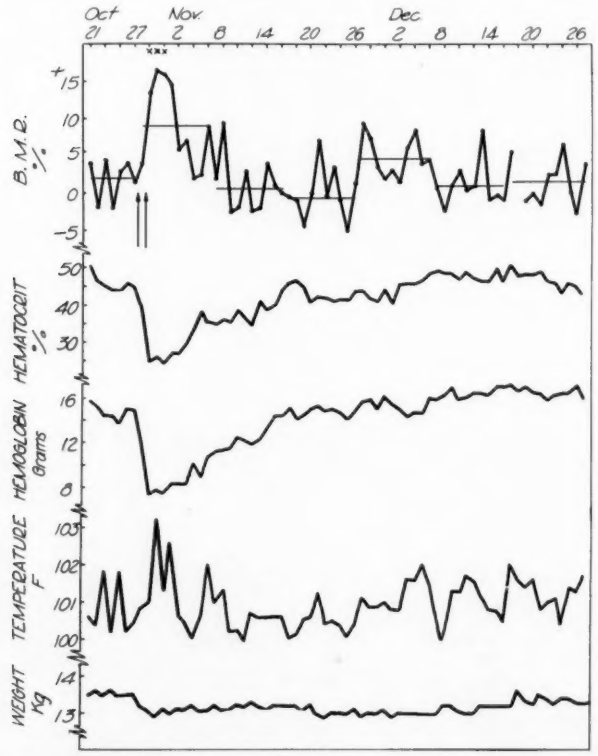

Chart 4 (dog 3).—Three hundred and eighty cubic centimeters of blood was drawn on October 27, and 330 cc. on October 28. The dog was acutely ill with fever, vomiting and anorexia for three days after the last bleeding. There was a loss of about 0.5 Kg. in weight. This result may be similar to those obtained by Hawk and Gies [9] in which there was loss of nitrogen following severe or repeated hemorrhages.

nitrogen after bleeding may be due to the "washing out" effect of the large amount of water consumed. The permanent occlusion of such

9. Hawk, P. B., and Gies, W. J.: The Influence of External Hemorrhage on Chemical Changes in the Organism, with Particular Reference to Proteid Catabolism, Am. J. Physiol. **11**:171, 1904.

large arteries as the femoral artery might be expected to lead to death of tissue and therefore actual catabolism of protein. Extensive and repeated hemorrhages may influence the dog's general metabolism adversely, while moderate hemorrhages would not. Although the metabolism of all three of the animals remained permanently lower after the bleeding, the following conclusion seems justifiable: During

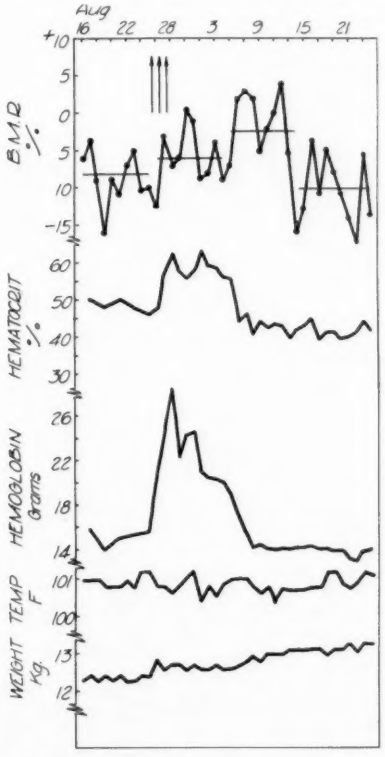

Chart 5 (dog 1).—Blood transfusions were given on August 25, 26 and 27. The amounts were 275, 190 and 155 cc., respectively, and in each instance 50 cc. of 2.5 per cent sodium citrate was used as an anticoagulant.

recovery from acute hemorrhagic anemia of moderate degree in dogs there is a decrease in oxygen consumption which is comparable with that seen in patients with pernicious anemia during the recovery which is induced by liver extract.

Transfusion of Whole Blood.—Dogs 1 and 4 were given transfusions of compatible whole blood in quantities equivalent to about

50 cc. per kilogram of body weight (charts 5, 6, 7 and 8 *B*). Transfusions were given to dog 1 on three successive days and were begun forty days after the previous experiment with bleeding. The weight, blood count and oxygen consumption had reached constant levels before the transfusions were given. Dog 4 had not been bled previously, and neither dog had been given a transfusion previously.

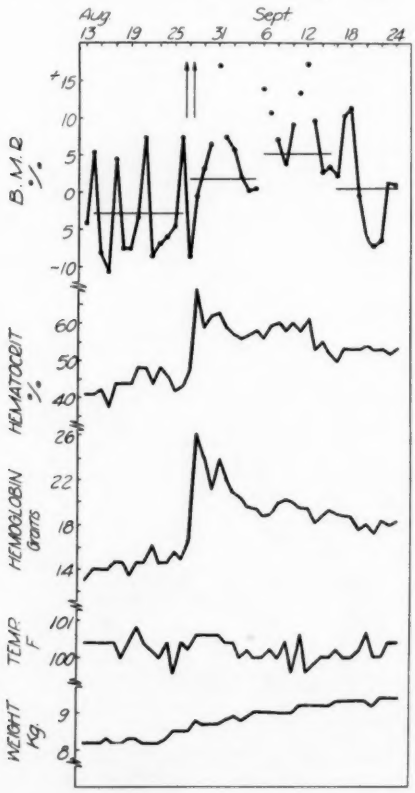

Chart 6 (dog 4).—Transfusions were made on Aug. 26 and 27, 1931. The amounts of blood given were 180 and 245 cc. Several determinations of basal metabolism were considered to be unsatisfactory because the dog moved. These rates are indicated by dots but are not connected by solid lines and were not used in computing averages.

The responses in the two dogs were parallel. There was an immediate increase in hemoglobin and hematocrit values and in erythrocyte counts. The hematocrit values remained fairly constant for ten days in dog 1 and for sixteen days in dog 4. The hemoglobin values seemed

to fall off gradually in both dogs, but the erythrocyte counts paralleled the hematocrit values rather well. Both dogs showed a greater loss of blood during the second period of ten days after transfusion than during the first period of ten days.

The basal metabolic rate increased as the volume of corpuscles decreased. For the first ten days after transfusion the basal metabolic rate was slightly above the control average, 2.3 per cent in dog 1 and

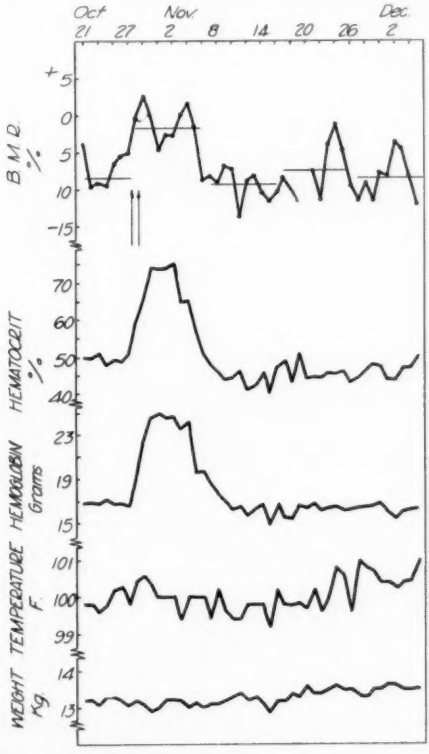

Chart 7 (dog 2).—Two hundred and sixty cubic centimeters of blood was given on October 27 and 330 cc. on October 28.

4.6 per cent in dog 4. In the second period of ten days the average basal metabolism was 6 per cent above the control in dog 1 and 8 per cent above the control in dog 4. In each dog, the blood count and the oxygen consumption returned approximately to normal during the third period of ten days after transfusion. It is admitted that the differences in basal metabolic rates in these experiments are slight, especially in view of the many variable factors influencing the determination of the

oxygen consumption by the method employed. However, the orderliness and parallelism of the changes in the two animals and especially the correlation between the oxygen consumption and the loss of blood are striking enough to appear significant. Changes in body temperature were slight and bore no apparent relation to the changes in oxygen consumption.

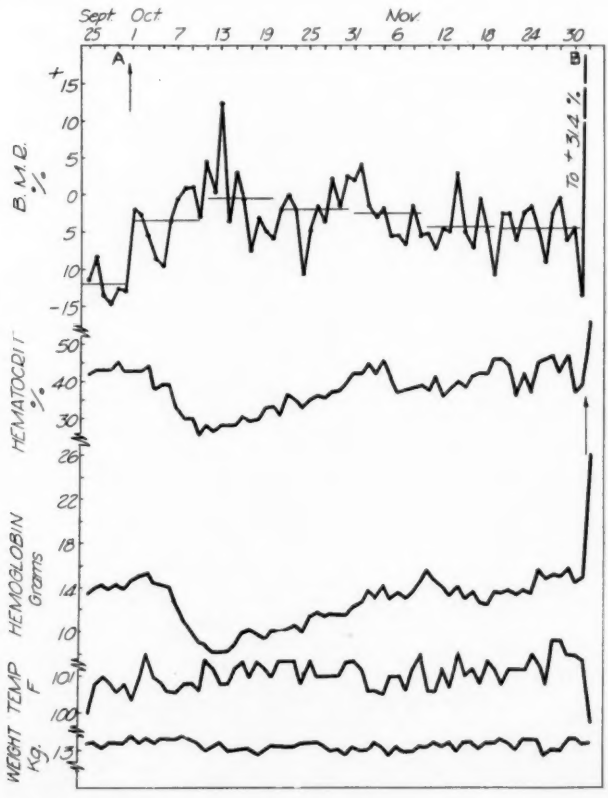

Chart 8 (dog 1).—*A*, 200 cc. of citrated plasma was given intravenously on September 30. *B*, 375 cc. of whole blood was given intravenously on Dec. 1, 1931. The dog died on December 2.

A similar experiment was performed in the case of dog 2, but conditions were different in one regard. On Sept. 1, 1931, dog 2 received subcutaneous injections of the plasma and hemolyzed corpuscles from 275 cc. of compatible blood. On September 30 a further injection of 265 cc. of citrated plasma was made intravenously. On October 27 and

28, dog 2 received transfusions totaling 590 cc. of whole blood from a different but compatible donor. This transfusion led to the usual immediate increase in the hemoglobin, volume of corpuscles and erythrocyte count, but loss of blood set in on the fifth day instead of after from ten to sixteen days, as had been the case in dogs which had not previously received transfusions. This earlier loss of blood was associated with an earlier increase in the basal metabolic rate. The average basal metabolic rate for the ten days following transfusion was 5.2 per

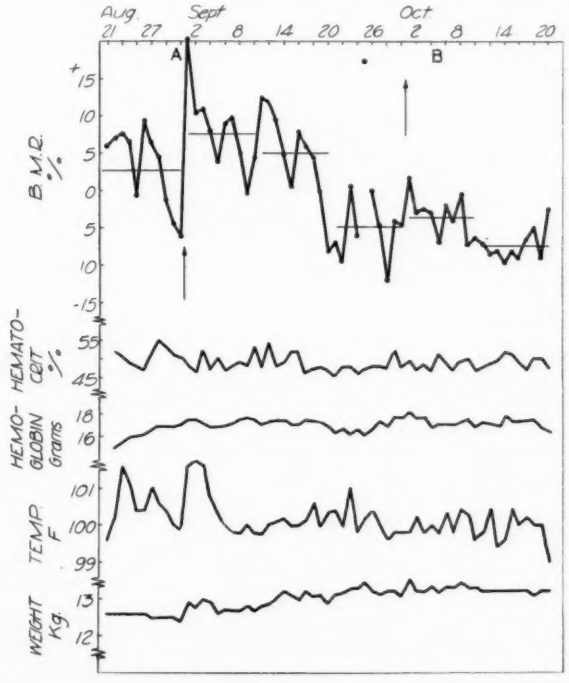

Chart 9 (dog 2).—*A*, the plasma and hemolyzed corpuscles from 275 cc. of blood were injected subcutaneously on September 1. *B*, 265 cc. of citrated plasma was administered intravenously on September 30.

cent above the control average. The average of the results of the determinations made during the second period of ten days showed that the gaseous metabolism was 2.4 per cent below the control average. The data in this experiment lend support to the assumption that there is a causal relationship between the loss of blood and the increase in oxygen consumption.

In an effort to study this process in a more accentuated form, dog 1 was given a transfusion of 375 cc. on Dec. 1, 1931. Previous trans-

fusions in the case of this dog included intravenous injections of whole blood in amounts of 275, 190 and 155 cc. on Aug. 25, 26 and 27, 1931, and an injection of 200 cc. of citrated plasma on September 30. All of the transfusions were made from the same donor, the blood of which was originally compatible.

The basal metabolism, which during the control period had averaged 4.5 per cent below normal, increased to 31.4 per cent above normal on the day after the transfusion. With this rise in the gaseous metabo-

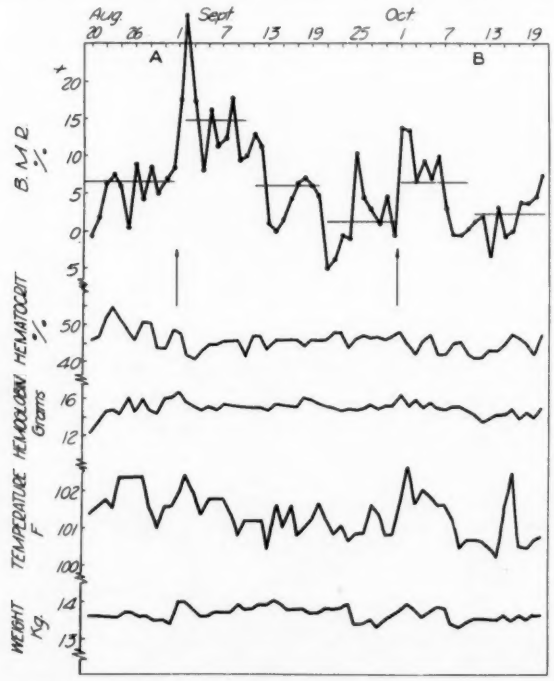

Chart 10 (dog 3).—*A*, the plasma and hemolyzed corpuscles from 325 cc. of blood were injected subcutaneously on September 1. *B*, the hemolyzed corpuscles from 320 cc. of blood were given subcutaneously on September 20.

lism the temperature dropped from 101.5 to 99.8 F. Later in the day the dog died. Necropsy revealed intense congestion of the spleen, liver and lymph nodes, with dark blood in the gastro-enteric tract and hemorrhages into most of the mucous surfaces. Paresis of the caudal half of the body, which appeared soon after the transfusion, was unexplained at necropsy.

Hemolyzed Corpuscles and Plasma.—In order to speed up the catabolism of the hemoglobin of transfused blood, hemolyzed erythro-

cytes were injected into two dogs (charts 9 *A*, 10 *A* and 11 *A*). The corpuscles were hemolyzed in distilled water, and plasma and hemolyzed corpuscles were injected subcutaneously. Dog 2 received 275 cc. of whole blood so treated, and dog 3 was given the plasma and hemolyzed corpuscles from 325 cc. of blood.

There was a prompt outpouring of blood pigments in the urine. The urine was black and gave positive qualitative tests for bile pigments and

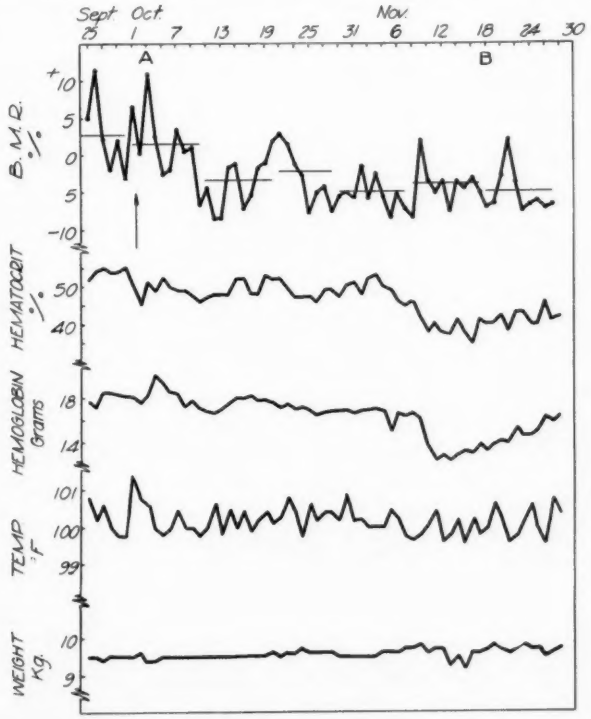

Chart 11 (dog 4).—*A*, the hemolyzed corpuscles from 275 cc. of blood were given on September 30. *B*, from October 28 to November 15 almost daily injections of distilled water were made intravenously. Thirty cubic centimeters was injected daily for ten days, after which injections of the following amounts were made each day: 100, 150, 200, 200, 200, 300, 300, 0.0 and 300 cc. Twice the basal metabolic rate was determined at hourly intervals after injections of 300 cc. (see text). Hemoglobin appeared in the urine after seven of the injections of distilled water.

for hemoglobin. There was also rather marked proteinuria. There was a slight increase in temperature, but in neither case did the temperature exceed the high point in the control period. Following the injec-

tions there was an abrupt rise in the oxygen consumption, which was followed by a gradual fall extending over the succeeding twenty days. The number of erythrocytes and the amount of hemoglobin in the recipient's blood were not affected by this procedure. The urine remained dark for several days.

In these, as in the preceding experiments, the increased oxygen consumption coincided with the period of assumed protein catabolism. Nitrogen balances, however, were not determined.

At a later date dogs 3 and 4 received injections of hemolyzed corpuscles without plasma (charts 10 *B* and 11 *A*). The amounts were smaller, hemoglobin from 180 cc. of blood injected into dog 3 and from 275 cc. of blood injected into dog 4. The results were similar to those in the preceding experiments except that the increase in oxygen consumption was less marked in spite of the fact that the increase in temperature was greater.

An attempt was made to study the effects of in vivo hemolysis by distilled water in dog 4 (chart 11 *B*). Distilled water was injected intravenously in amounts varying from 30 to 300 cc. Hemoglobin appeared in the urine on seven occasions, and there was a loss of about 5 Gm. of hemoglobin per hundred cubic centimeters of blood during a period of nine days. However, the oxygen consumption as determined twenty-two hours after the injections remained normal. On two days determinations made at hourly intervals after the injections showed maximum increases of 14 and 69 per cent. On the second day the increase lasted at least ten hours, but there were a chill and an elevated temperature which invalidated the result. On the first day, which presents no doubt the more accurate picture of the changes, the control basal metabolic rate was 3.5 per cent below normal. After the rapid injection of 300 cc. of warm distilled water the rates at hourly intervals were as follows: plus 10.4, plus 9.4, plus 8.7, plus 8.9, plus 2.3 and plus 6.4 per cent. Here, as in the preceding experiments, hemoglobinuria was accompanied by proteinuria. It is recognized, of course, that the nitrogen appearing in the urine as protein or amino-acids must be deducted from the total nitrogen in order to estimate catabolized protein nitrogen.

Plasma Administered Intravenously.—Citrated plasma was injected intravenously in dogs 1 and 2 (charts 8 *A* and 9 *B*). The results were in part unexpected. Dog 2 received 265 cc. of citrated plasma on Sept. 30, 1931. On the day following the injection, the oxygen consumption was about 6 per cent greater than on the day preceding the transfusion, while the average for the ten days following transfusion was about 1 per cent higher than the control average. The hemoglobin, hematocrit value and erythrocyte count were unaffected by this pro-

cedure. The dog had had only one previous injection of plasma and hemolyzed corpuscles from the same donor.

The case of dog 1 was different (chart 8 *A*). Intravenous injection of 200 cc. of citrated plasma was made as in dog 2. The basal metabolic rate, which was 13 per cent below normal on the day before the injection, was only 2 per cent below normal on the following day. The average oxygen consumption for the first ten days after the injection of plasma was 8.5 per cent above the control level, while the average for the second period of ten days was 11.5 per cent above the control level. This increase in oxygen consumption was associated with a loss of hemoglobin from about 15 to about 8 Gm. per hundred cubic centimeters of blood and a corresponding decrease in hematocrit value and erythrocyte count. Unfortunately, estimations of the urobilin and urobilinogen content of the stools and urine and nitrogen balances were not made, so that it is not possible to attribute the loss of blood definitely to hemolysis. Recovery of the blood elements was complete, however, a circumstance which makes it unlikely that the loss of blood was due to aplasia of the bone marrow.

In these experiments it appears that destruction of blood was produced in one animal and not in the other. It further appears that a rather nicely controlled experiment showing the effect of the destruction of blood on the total oxygen consumption has been unwittingly accomplished. The results are in complete accord with the general thesis, i. e., that the oxygen consumption is increased by increased endogenous protein catabolism.

Diabetes Caused by the Administration of Phlorhizin.—Phlorhizin diabetes seemed to present the most ideal situation for putting the previously suggested general thesis to a crucial test (charts 12, 13 and 14). In the phlorhizinized animal endogenous protein catabolism proceeds at a greater rate than in any other nonfatal condition that I know. As the effects of phlorhizin disappear, the animal is left in good health, except that his protein is much depleted. Such a condition should therefore be ideal for the study of the effects of endogenous protein catabolism as well as of the effects of marked retention of nitrogen in the laboratory animals. It was demonstrated by Rubner [10] that the specific dynamic effect of catabolized protein of endogenous origin could account for the marked increase in oxygen consumed by the fasting phlorhizinized dog. From such calculations Lusk concluded that protein of endogenous origin exerts the same specific dynamic effect as a similar amount of exogenous protein. To my knowledge, no one has previously studied the oxygen consumption of animals during the period of nitrogen storage in the recovery from diabetes due to the administration of phlorhizin.

10. Rubner, M.: Die Gesetze des Energie verbrauchs bei der Ernährung, Leipzig, Franz Deuticke, 1902, p. 370; quoted by Lusk,[6] p. 282.

Dog 2 was given the regular diet up to and including Dec. 15, 1931. After the determination of the basal metabolism on December 16, 1 Gm. of phlorhizin was injected subcutaneously. No more food was given for eight days, during which there was evidence of marked endogenous protein catabolism. The D: N ratio reached only 1.93, so that the animal was not completely phlorhizinized. On December 24, food, consisting of 225 Gm. of bread, 250 cc. of milk and 20 Gm. of bone meal or 4.6 Gm. of nitrogen, was allowed. The oxygen con-

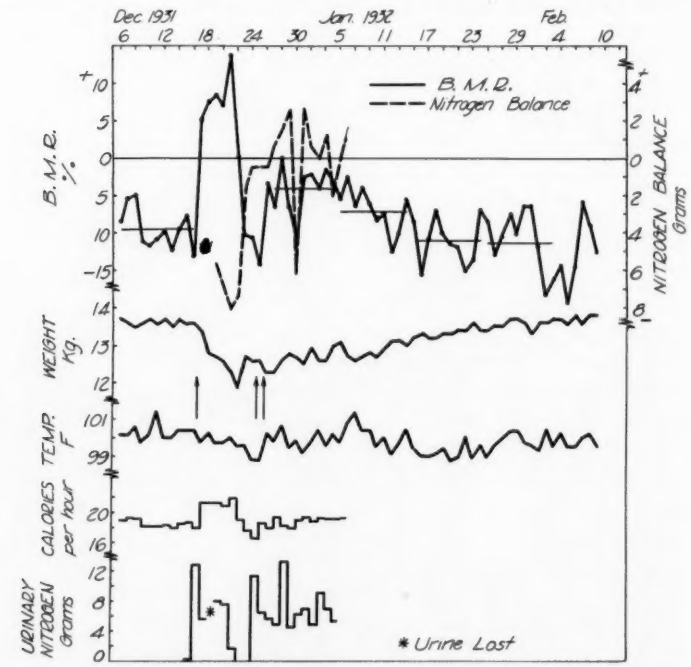

Chart 12 (dog 2).—The first arrow (from left to right) indicates the beginning of the fast and the administration of 1 Gm. of phlorhizin subcutaneously on December 16. The second arrow indicates when food was first given, on December 24, 225 Gm. of bread, 250 cc. of milk and about 20 Gm. of bone meal. The third arrow indicates the return to the normal diet. The nitrogen balance is not accurate, since fecal nitrogen and the nitrogen lost in hair were not determined. The irregularity in the output of urinary nitrogen was caused by the fact that the dog had been conditioned not to urinate in a cage.

sumption, which had been falling to about parallel with the fall in nitrogen catabolism, continued to fall with the ingestion of the aforementioned amount of protein. From December 25 to the end of the experiment the animal was given its regular diet of 150 Gm. of chopped

raw beef lung, 225 Gm. of bread, 250 cc. of milk and 20 Gm. of bone meal, a total of 6.8 Gm. of nitrogen daily. After the return to a normal diet there was an immediate increase in the amount of urinary nitrogen with a similar increase in gaseous metabolism (chart 12). Nitrogen retention was not constant or marked. It seemed evident that the animal was continuing to break down protein instead of storing it. This

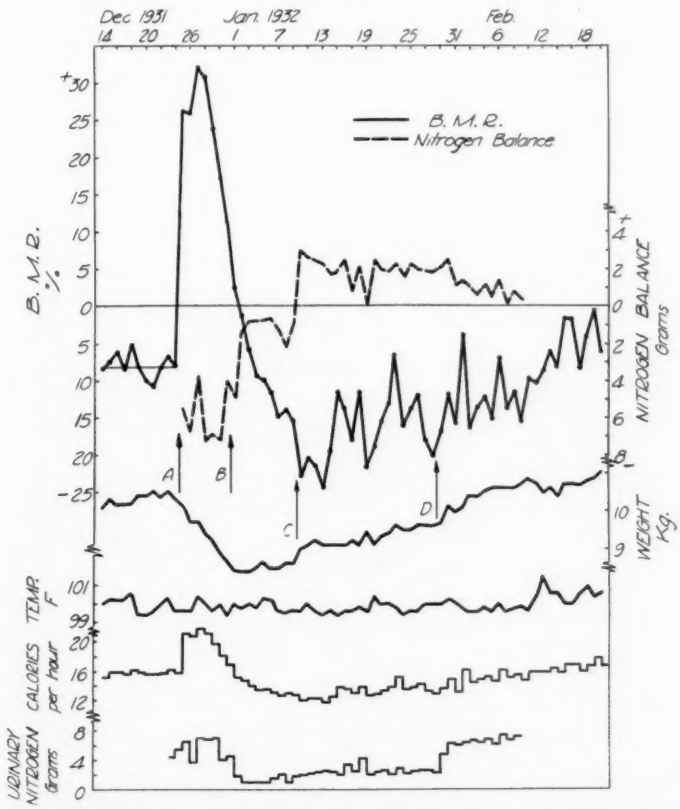

Chart 13 (dog 4).—Arrows indicate the following: *A*, subcutaneous injection of 1 Gm. of phlorhizin and the beginning of the fast; *B*, from 50 to 200 Gm. of sugar daily (total 1,050 Gm.); *C*, 200 Gm. of bread, 20 cc. of milk and about 20 Gm. of bone meal daily; *D*, 200 Gm. of meat was added to the diet. Again the nitrogen balance did not include nitrogen lost in the feces or hair.

may have been due to the fact that the stores of glycogen were empty when realimentation with a mixed diet occurred. An attempt was made to control this factor in the succeeding experiments.

In the case of dog 4 (chart 13) the procedure was the same, except that on the seventh day after phlorhizin was administered, 50 Gm. of dextrose was given by mouth. On the six succeeding days the animal received 100 Gm. of dextrose daily and then 200 Gm. daily for two days. During this time the gaseous metabolism and the urinary nitrogen continued to decrease. The average basal metabolic rate during the

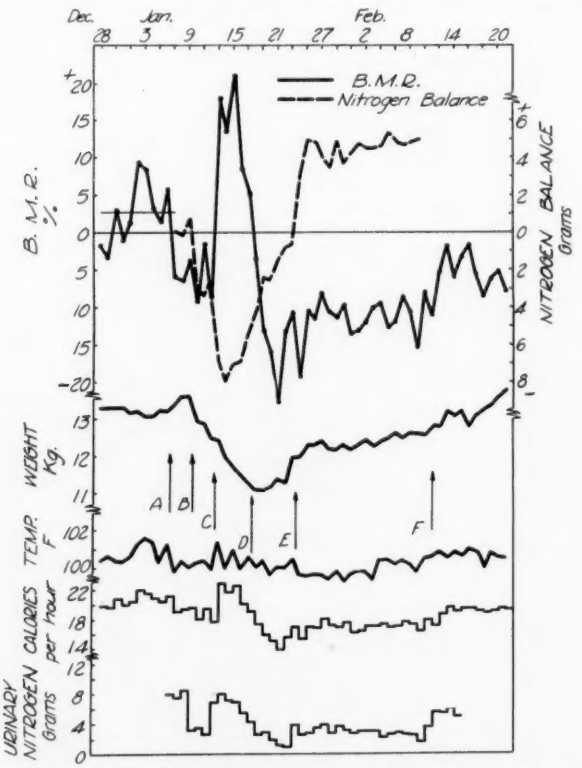

Chart 14 (dog 3).—The arrows indicate the following: *A*, the dog was moved from regular animal quarters to the cage in the metabolism room; *B*, the fast was begun; *C*, 1 Gm. of phlorhizin was given; *D*, from 100 to 300 Gm. of sugar (total, 2,000 Gm.) was given; *E*, 300 Gm. of bread, 350 cc. of milk and 20 Gm. of bone meal were given daily; *F*, 200 Gm. of meat was added.

control period was 8.1 per cent below normal. During the period of increased protein catabolism after phlorhizin the metabolic rate reached 32.1 per cent above normal, but the oxygen consumption fell to 15.5 per cent below normal, as endogenous protein was spared by the feeding of sugar. On December 9 the diet was changed to 200 Gm. of bread,

250 cc. of milk and 20 Gm. of bone meal or 4.56 Gm. of nitrogen a day. This diet was attended by marked and consistent nitrogen retention and a further fall in the oxygen consumption to 24.4 per cent below normal. This second fall in gaseous metabolism which occurred when the animal was receiving a diet low in proteins is not understood, since the actual amount of nitrogen in the urine was greater than it had been on the preceding days when only carbohydrate was contained in the diet. Special attention is directed to the fact that in this animal the basal metabolic rate fell from plus 32.1 to minus 24.4 per cent, a total excursion of 56.5 per cent, without change in temperature. The decrease from plus 32.1 to minus 15.5 per cent appeared to be caused entirely by a drop in the catabolism of endogenous protein.

In dog 3 the procedure and results were almost exact duplicates of those in dog 4 (chart 14).

The following explanation is offered for the results in all of the experiments described:

Endogenous protein, when catabolized, exerts the same specific dynamic effect as would a similar amount of ingested protein. The difference is that the effect of exogenous protein can be avoided to a great extent by making determinations of the basal metabolic rate only in the postabsorptive period. Endogenous protein catabolism, on the other hand, is a continuous process, and some of the animo-acids so derived exert their effect throughout the day.

The explanation for the lowered gaseous metabolism during the storage of nitrogen is not quite so clear but no doubt depends in part at least on the fact that stored amino-acids exert no specific dynamic effect. From numerous data it seems probable, though not proved, that the lowered oxygen consumption during the storage of nitrogen is due not so much to the storage of nitrogen per se as to a lowered total endogenous catabolism of protein during the postabsorptive period when storage is in progress.

Numerous data in the literature support this thesis directly or indirectly. Only a few will be mentioned. Rubner [11] and Hoobler [12] independently showed that stored protein does not exert a specific dynamic effect. Lee and Gagnon [13] showed that rats growing rapidly under the influence of the growth-promoting hormone from the anterior pituitary lobe have a lowered basal metabolism as referred to weight or surface area. The realimentation following a fast is not attended

11. Rubner,[10] p. 246, quoted by Lusk,[6] p. 297.

12. Hoobler, B. R.: The Protein Need of Infants, Am. J. Dis. Child. **10**:153 (Sept.) 1915.

13. Lee, M. O., and Gagnon, J.: Effect of Growth Promoting Extracts of the Anterior Pituitary on Basal Gaseous Metabolism in Rats, Proc. Soc. Exper. Biol. & Med. **28**:16, 1930.

by an immediate return of the oxygen consumption to the prefasting level (Kleitman [14] and Anderson and Lusk [15]).

Evidence that increased protein catabolism is associated with an augmented gaseous metabolism is also to be found in the literature. Du Bois [16] and his co-workers demonstrated that the increased oxygen consumption in febrile diseases was more or less proportional to the degree of endogenous protein catabolism which was present. For example, for a given elevation in temperature typhoid fever usually presented a greater protein catabolism and a greater oxygen consumption than did pulmonary tuberculosis. Similarly, increases in endogenous protein catabolism [17] and in oxygen consumption occur coincidentally in the first few days of a fast and possibly during the premortem rise in nitrogen excretion. Wilder, Boothby and Beeler [18] demonstrated a definite relationship in diabetes between the amount of protein in the diet and the basal metabolism. Heinbecker [19] found that the gaseous metabolism of Eskimos was considerably higher than that of people living in the temperate zone. At the Russel Sage Institute [20] two Arctic explorers were kept on a diet of meat for a year. After six weeks the basal metabolism had increased slightly, but at the end of a year it was back to the level which had been observed for a mixed diet. There was a suggestion that the specific dynamic action of protein increased after long periods on diets of meat. In most instances the diets were much higher in fat than in protein. There is a possibility, of course, that the presence of acetone influenced the results obtained by the investigators, who studied subjects receiving diets high in fat and relatively high in protein but without carbohydrate.

SUMMARY

1. In pernicious anemia the basal metabolic rate decreases during periods of rapid regeneration of blood.

2. In leukemia the total oxygen consumption is increased during the increased catabolism of endogenous protein induced by irradiation.

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14. Kleitman, N.: Basal Metabolism in Prolonged Fasting in Man, Am. J. Physiol. **77**:233, 1926.

15. Anderson, R. J., and Lusk, G.: Animal Calorimetry: The Interrelation Between Diet and Body Condition and the Energy Production During Mechanical Work, J. Biol. Chem. **32**:421, 1917.

16. Du Bois, E. F.: The Basal Metabolism in Fever, J. A. M. A. **77**:352 (July) 1921.

17. Lusk,[6] p. 78.

18. Wilder, R. M.; Boothby, W. M., and Beeler, C.: Studies of the Metabolism of Diabetes, J. Biol. Chem. **51**:311, 1922.

19. Heinbecker, P.: Studies on the Metabolism of Eskimos, J. Biol. Chem. **80**:461, 1928.

20. McClellan, W. S.; Spencer, H. J., and Falk, E. A.: Clinical Calorimetry: XLVII. Prolonged Meat Diets with a Study of the Respiratory Metabolism, J. Biol. Chem. **93**:419, 1931.

3. The destruction of erythrocytes by phenylhydrazine in polycythemia vera is attended by an increase in gaseous metabolism.

4. In dogs the oxygen consumption is decreased during recovery from moderately severe acute hemorrhagic anemia.

5. Compatible blood transfused into dogs is lost from the peripheral circulation at varying rates. The rapidity of loss of blood seems to be increased in successive transfusions. The basal metabolic rate of the dog is increased during the period of loss of blood.

6. The pigment from hemolyzed blood is rapidly excreted by dogs, and again the catabolic process is attended by an increase in gaseous metabolism. The increased metabolism occurs whether the blood is hemolyzed in vivo or is obtained from another animal.

7. The injection of citrated plasma into dogs is sometimes attended by a delayed loss of blood in the recipient, and this loss of blood appears to cause an increase in gaseous metabolism.

8. Phlorhizin diabetes in the dog is associated with a great increase in endogenous protein catabolism which is followed under certain conditions by marked storage of nitrogen. The oxygen consumption in the phlorhizinized animal parallels the endogenous protein catabolism.

HEPATIC FUNCTION

I. NONCALCULOUS AND CALCULOUS CHOLECYSTITIS

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PHILADELPHIA

Increasing recognition of the valuable information which may be derived from studies of hepatic function has resulted in the accumulation of a large quantity of data in this connection in recent years. In my experience, however, too little emphasis has been placed on such studies in the field in which they are of greatest value, namely, in the preoperative study of patients with disease of the gallbladder and bile ducts. This point was stressed in a previous report [1] of a study of 234 patients with calculous and noncalculous cholecystitis, 70 of whom presented hyperbilirubinemia or bromsulphalein retention or both. The present report is a continuation of that study, with a more detailed presentation of the findings in a much larger series of patients.

During the years from 1931 to 1933, various studies of hepatic function were performed in 512 cases of cholecystitis and cholelithiasis; 49 of these were acute noncalculous cholecystitis, 288, chronic noncalculous cholecystitis, and 138, calculous cholecystitis, and in 37 cases, stones were present in the common bile duct. Of the several observations that were made, only the following are included: (1) qualitative van den Bergh reaction, (2) serum bilirubin concentration (quantitative van den Bergh method), (3) bromsulphalein retention (dosage of 2 mg. per kilogram expressed as thirty minute retention), (4) plasma cholesterol concentration (method of Myers and Wardell) and (5) urinary urobilinogen (method of Wallace and Diamond). In my experience, the normal range of values by the methods employed are as follows: bromsulphalein retention, 0 per cent; plasma cholesterol, from 140 to 200 mg. per hundred cubic centimeters; urobilinogen in urinary dilution to 1:20, serum bilirubin concentration, from 0.1 to 1 mg. per hundred cubic centimeters of serum or plasma. I think that the normal serum bilirubin values usually quoted in the literature are far too low. The most frequent source of error lies in the fact that unless the test is carefully performed according to the procedure suggested by Thannhauser and Andersen, varying quantities of bilirubin are adsorbed by the protein precipitate and are consequently eliminated from the calculation. In a large series of determinations on normal persons I obtained the following results: from 0.1 to 0.5 mg. in about

From the Laboratory of Biochemistry, Jefferson Hospital.

1. Cantarow, A.: The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, Am. J. M. Sc. **184**:228, 1932.

60 per cent, from 0.51 to 0.8 mg. in about 35 per cent and from 0.81 to 1 mg. in about 5 per cent. Another point in this connection deserves special emphasis. Hunter [2] and later Rabinowitch [3] called attention to an error in the original calculation of the van den Bergh unit. Rabinowitch stated that:

> The color of the original artificial standard which was meant to match that produced by 1 unit of bilirubin corresponded to that obtained with a mixture of 10 cc. of alcohol, 2.5 cc. of diazo reagent and 0.05 mg. of bilirubin. Since 12.5 cc. of solution contained 0.05 mg. of bilirubin, the true unit corresponds to a 1:250,000 and not to a 1:200,000 dilution of bilirubin. Expressed more exactly, the true unit corresponds to 0.4 and not 0.5 mg. of bilirubin per 100 cc. of blood.

TABLE 1.—*Acute Cholecystitis*

Case	Date	Direct Van den Bergh	Serum Bilirubin*	Bromsulphalein Retention†	Plasma Cholesterol*	Urobilinogen in the Urine
1	4/ 7/32	0	1.6	0	162	1:10
	4/11/32 Operation	+	6.0	90	...	0
	4/14/32	0	1.12	0	146	1:30
2	.....	+	1.5	0	...	1:10
3	.....	+	9.1	80	122	1:60
4	.....	+	1.3	60	104	
5	.....	0	0.9	5	150	
6	.....	+	2.05	100	126	0
7	12/ 1/32	+	2.0	50	125	1:40
	12/ 7/32	0	0.2	0		
8	.....	0	0.65	5		
9	4/ 4/33	0	0.8	25	256	
	4/ 9/33	0	0.4			
10	.....	0	1.94	0		
11	4/18/33	+	4.25	50	274	1:30
	4/25/33	+	6.0	90		
	5/ 2/33	+	2.5	5		
	5/19/33	0	0.6	0		
12	11/ 8/33	0	0.96	20		
	11/14/33	0	0.52	0	...	1:20
13	.....	0	0.16	15	150	1:10

Cases	Serum Bilirubin*	Bromsulphalein Retention†	Plasma Cholesterol*	Urobilinogen in the Urine
36	0.12-0.88	0	124-196	0-1:20

* Expressed in milligrams per hundred cubic centimeters.
† Expressed as percentage.

This obvious error has apparently been overlooked by the great majority of workers in this field.

EXPERIMENTAL RESULTS

Acute Cholecystitis.—In the group of 49 cases of acute cholecystitis, essentially normal findings were obtained by all methods in 36 instances, with the exception of slightly subnormal cholesterol values (from 124 to 132 mg.) in 4 cases. Disturbance of hepatic function was suggested by one or more of the methods employed in 13 cases in this group (26.5

2. Hunter, G.: The Determination of Bilirubin by Diazo Reagents, Brit. J. Exper. Path. **11**:407, 1930.

3. Rabinowitch, I. M.: The Renal Threshold of Bilirubin, J. Biol. Chem. **97**: 163, 1932.

per cent). The detailed findings are presented in table 1. Hyperbilirubinemia (from 1.3 to 6 mg.) was present at some time in 8 cases; bromsulphalein retention in 11; hypercholesteremia in 2; hypocholesteremia in 4 and urobilinuria in 4. The occurrence of hyperbilirubinemia without retention of dye was noted in 3 cases, and retention of dye without hyperbilirubinemia in 5 cases.

TABLE 2.—*Chronic Cholecystitis: Cases with Retention of Bromsulphalein Without Hyperbilirubinemia*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	.....	0	0.9	10	...	1:20
2	.....	0	0.83	80	136	1:40
3	.....	0	0.37	10	117	
4	.....	0	0.5	10		
5	.....	0	0.69	60	121	1:50
6	.....	0	0.72	5		
7	.....	0	0.4	5		
8	.....	0	0.98	10	185	1:20
9	.....	0	0.74	5		
10	.....	0	0.37	5	...	1:10
11	1/20/33	0	0.8	100		
	1/22/33	0	0.4	5		
12	.....	0	0.8	10	228	
13	.....	0	0.8	5		
14	.....	0	0.82	20		
15	.....	0	0.65	5	124	
16	1/24/33	0	0.4	10		
	1/30/33	0	0.35	0		
17	.....	0	0.8	5	123	
18	.....	0	0.6	10	146	
19	.....	0	0.9	10	192	
20	.....	0	0.4	10		
21	.....	0	0.9	5		
22	3/ 7/33	0	0.6	5	224	
	4/19/33	+	1.5	5		
	5/ 3/33	+	7.5	100	198	
	5/ 9/33	+	2.7	5		
23	.....	0	0.7	5	148	
24	.....	0	0.3	5	135	
25	.....	0	0.7	5		
26	.....	0	0.8	25	148	0
27	.....	0	0.5	20	186	1:20
28	.....	0	0.51	10		
29	.....	0	0.64	25	73	1:60
30	.....	0	0.24	10	148	1:20
31	.....	0	0.69	10	192	
32	.....	0	0.81	20	136	1:40

Chronic Noncalculous Cholecystitis.—Essentially normal findings were obtained in 212 of 288 patients with chronic noncalculous cholecystitis (table 5). Evidence suggestive of hepatic functional impairment was noted in 76 cases in this group (26.3 per cent). Retention of bromsulphalein (from 5 to 100 per cent) without hyperbilirubinemia was present at some time in 32 cases (table 2); hyperbilirubinemia (from 1.1 to 3 mg.) and retention of dye (from 5 to 100 per cent) in 29, and hyperbilirubinemia (from 1.08 to 1.5 mg.) without retention of dye, in 15 cases. Hypercholesteremia (from 224 to 279 mg.) was noted in 4, hypocholesteremia (from 73 to 136 mg.), in 15, and urobilinuria (from 1:30 to 1:200), in 16 cases.

TABLE 3.—*Chronic Cholecystitis: Cases with Retention of Bromsulphalein and Hyperbilirubinemia*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom-sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	.....	0	1.1	10		
2	8/31/32	+	2.2	45	136	1:80
	9/ 5/32	0	0.63	5		
3	.....	0	1.16	10	164	1:10
4	.....	0	1.12	15	144	
5	.....	0	1.45	5		
6	5/22/32	+	3.0	25	184	1:200
	6/ 8/32	0	0.81	10	...	1:100
7	.....	0	1.3	30		
8	.....	0	1.2	10	126	1:20
9	1/ 4/33	+	1.8	40	...	1:100
	1/10/33	0	0.3	5		
10	.....	0	1.1	5	174	0
11	.....	0	1.57	5	...	1:30
12	.....	0	1.1	5	...	1:10
13	.....	+	1.6	30		
14	.....	+	2.5	20	...	1:20
15	.....	0	1.1	5	163	
16	.....	0	1.1	100		
17	.....	+	1.7	50		
18	.....	+	1.2	20	128	1:40
19	.....	+	2.0	10		
20	.....	0	1.3	10	147	1:75
21	.....	+	1.8	20	...	1:40
22	.....	0	1.4	10	154	
23	.....	0	1.2	10	...	1:40
24	.....	+	2.1	10		
25	.....	0	1.6	20	141	1:60
26	.....	+	1.9	10	168	
27	.....	+	2.4	30		
28	.....	+	2.3	40	106	1:80
29	.....	0	1.3	10	...	1:20

TABLE 4.—*Chronic Cholecystitis: Cases with Hyperbilirubinemia without Retention of Bromsulphalein*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom-sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	.....	0	1.08	0	161	1:10
2	.....	0	1.43	0		
3	.....	0	1.2	0	95	1:20
4	.....	0	1.2	0	272	1:20
5	.....	0	1.5	0		
6	.....	0	1.2	0		
7	.....	+	1.2	0	197	
8	.....	0	1.1	0	279	
9	5/13/33	0	1.2	0		
	5/19/33	0	0.5	10		
10	.....	0	1.2	0		
11	.....	0	1.12	0	104	1:40
12	.....	0	1.3	0		
13	.....	0	1.1	0	174	1:20
14	.....	0	1.46	0	189	
15	.....	0	1.28	0	162	1:10

TABLE 5.—*Chronic Cholecystitis: Cases with Essentially Normal Findings*

Cases	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
212	024-0.91	0	134-200	0-1:40

TABLE 6.—*Calculous Cholecystitis*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	1/ 5/32	+	4.0	20	194	1:20
	1/ 9/32	+	2.0	0		
2	.....	+	2.2	35	121	
3	1/23/32	+	1.2	90		
	1/28/32	+	4.04	100	106	1:100
	3/ 9/32	0	0.6	0		
4	1/29/32	0	1.32	0	93	1:30
	2/ 4/32	0	1.08	0		
5	.....	+	3.2	100	...	1:50
6	2/ 3/32	+	2.68	55	119	
	2/10/32	0	0.52	0		
7	2/23/32	+	1.28	15	93	1:20
	2/28/32	0	0.75	0	102	
	3/ 1/32	+	1.16	5		
	3/21/32	0	0.44	5	120	
8	4/11/32	0	0.25	60	172	
	4/19/32	0	0.3	0		
9	8/ 3/32	+	2.4	15	258	1:60
	8/14/32	+	3.6	55		
	8/19/32	+	1.84	30		
	8/21/32	0	1.04	15		
	8/24/32	0	1.04	5	...	1:10
10	.....	0	0.43	10	147	
11	6/29/32	+	3.2	80	141	0
	7/ 5/32	0	1.08	0		
12	7/ 3/32	+	4.4	50	148	1:200
	7/14/32	0	0.64	5		
	7/20/32	0	0.53	0		
13	.....	+	4.4	20	164	1:10
14	.....	+	4.2	60		
15	.....	+	2.48	20		
16	5/10/32	+	5.2	100	101	
	5/16/32	0	1.01	0		
17	.....	0	1.4	50	106	
18	.....	0	2.4	0	142	
19	.....	0	1.0	100		
20	.....	+	3.1	80	105	1:25
21	.....	+	1.9	25	...	1:50
22	.....	0	0.9	10	211	
23	.....	+	3.1	5		
24	.....	0	1.5	0	188	
25	.....	+	3.1	60	122	1:40
26	.....	+	1.8	10	158	
27	.....	+	2.1	20		
28	.....	0	0.88	5	186	
29	.....	0	0.84	10	165	
30	.....	0	1.1	5	168	
31	.....	0	0.7	10	281	
32	1/18/33	+	4.0	100	181	1:150
	1/24/33	+	6.0	100	...	1:50
	2/ 1/33	+	1.87	40		
33	.....	+	2.05	40	...	1:40
34	.....	+	1.5	0	...	1:20
35	.....	0	0.4	5	216	
36	.....	+	2.3	10	195	1:10
37	.....	0	0.8	10	104	1:10
38	3/28/33	0	0.52	30	253	1:20
	4/ 4/33	0	0.4	5	...	0
39	.....	0	1.6	0		
40	.....	0	1.1	0		
41	.....	+	1.4	5	152	0
42	.....	0	1.2	0		
43	5/31/33	+	17.1	100	112	0
	7/ 5/33	0	0.75	0		
44	.....	+	4.25	100	226	1:10
45	.....	+	2.5	70	94	
46	.....	+	4.8	80	128	0
47	7/15/33	+	8.3	60		
	7/28/33	0	1.25	40	132	
	8/ 8/33	0	0.42	0		
48	7/26/33	0	1.1	50	...	1:40
	8/ 4/33	+	3.65	40	...	1:60
49	.....	+	1.75	20	...	0
50	.....	+	2.4	60	116	1:50
51	.....	0	1.8	0	...	1:50
52	.....	0	1.6	10	144	
53	.....	+	2.4	60	...	1:80
54	.....	+	2.6	40	182	
55	.....	0	1.2	10	193	
56	.....	+	3.1	80	...	1:60
57	.....	0	1.1	10	164	
58	.....	+	1.9	0		
59	.....	+	2.3	20		
60	.....	+	3.5	10		
61	.....	0	0.8	40	172	

Cases	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
77	0.14-0.98	0	152-234	0-1:20

TABLE 7.—*Stone in the Common Bile Duct*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	.....	+	3.5	10	...	1:10
2	1/26/32	+	5.16	100	276	1:10
	2/ 8/32	+	22.8	90		
	2/15/32	+	13.2	60		
	2/27/32	+	5.7	80	200	
	3/ 9/32	+	1.3	30	250	
	3/15/32	0	1.12	10	...	1:60
3	2/27/32	+	41.6	100	366	0
	3/ 9/32	+	23.0	100	480	
	3/17/32	+	21.6	100	526	
	3/29/32	+	14.4	100	400	
	4/10/32	+	18.0	100	404	
	4/28/32	+	4.4	60	408	1:100
	5/ 8/32	+	4.4	90		
	5/15/32	+	1.5	80	200	
	5/22/32	+	5.6	80		
	5/29/32	+	1.3	15	388	
	5/30/32	+	1.26	0	...	1:80
	7/14/32	0	0.88	0	276	
4	.....	0	0.6	80	242	
5	4/25/32	+	18.4	80	694	0
	5/ 1/32	+	13.0	60		
	5/ 8/32	+	2.03	0		
	5/15/32	0	2.1	0	288	1:60
	5/22/32	0	1.5	0	140	
6	5/ 8/32	+	19.0	100	...	1:10
	5/15/32	+	6.2	60	211	
	5/22/32	+	3.0	50		
	5/29/32	+	2.6	50	347	1:100
	6/ 6/32	0	1.0	10	258	
7	.....	+	11.2	30	202	0
8	9/26/32	0	2.9	0	200	1:60
	10/ 5/32	0	1.28	0		
	10/14/32	0	0.81	10		
	10/16/32	+	13.8	80	244	0
9	.....	+	26.0	100		
10	.....	+	36.8	100	...	0
11	.....	+	4.2	40	...	1:20
12	10/ 6/32	+	7.1	80	...	1:10
	10/15/32	+	9.3			
	10/20/32	+	6.8			
13	.....	+	4.8	15	245	
14	.....	+	11.2	100	206	0
15	.....	+	8.1	..	184	0
16	.....	+	7.5	..	209	0
17	.....	+	6.0			
18	.....	+	12.0	100		
19	.....	+	5.32	80	186	1:10
20	.....	+	6.0	70	224	
21	1/ 8/33	+	4.3	30	...	0
	1/15/33	+	8.5	80	...	0
22	.....	+	7.5	40	241	
23	4/ 8/33	+	3.0	20	178	
	4/12/33	0	0.84	0		
24	.....	+	10.0	80		
25	7/25/33	+	8.5	100	168	1:10
	7/29/33	+	6.5	80		
	8/ 2/33	+	5.8	65		
	8/15/33	+	3.0	15	...	1:50
26	.....	+	3.9	60	168	
27	.....	+	6.0	80	100	
28	.....	+	13.3	100		
29	.....	+	5.2	100		
30	6/23/33	+	11.0	..	...	0
	7/ 1/33	+	8.0	80		
	7/11/33	+	10.0	60		
	7/18/33	+	9.0	90		
	7/25/33	+	9.0	80		
	8/ 1/33	+	4.5	70	210	1:10
31	6/20/33	+	12.0	100	94	1:100
	7/26/33	0	1.0	0	126	1:20

Cases	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
6	0.64-0.98	0	169-192	1:10-1:20

Calculous Cholecystitis.—Evidence suggestive of hepatic functional impairment was obtained in 61 of 138 cases (44.8 per cent) of calculous cholecystitis without stones in the common bile duct (table 6). Retention of bromsulphalein (from 5 to 100 per cent) was present in 52 cases; hyperbilirubinemia (from 1.1 to 17.1 mg.), in 50; hypercholesteremia (from 211 to 281 mg.), in 7; hypocholesteremia (from 93 to 132 mg.), in 15, and urobilinuria (from 1:25 to 1:200), in 15 cases.

Stone in the Common Bile Duct.—Abnormal findings were obtained in 31 (83.7 per cent) of 37 patients with stone in the common duct (table 7). Retention of bromsulphalein (from 10 to 100 per cent) was present in 28 cases; hyperbilirubinemia (from 1 to 26 mg.), in 30; hypercholesteremia (from 202 to 694 mg.), in 13; hypocholesteremia (from 94 to 100 mg.), in 2, and urobilinuria (from 1:50 to 1:100), in 7 cases.

COMMENT

Noncalculous Cholecystitis.—Obviously, because of the location of the pathologic lesion, hyperbilirubinemia cannot result from uncomplicated cholecystitis. The occurrence of this phenomenon in association with noncalculous cholecystitis is dependent on the development of one or more of several complicating factors, among which are cholangitis, pancreatitis, hepatitis, spasm of the hepatic or common ducts, enlargement of the lymph nodes and obstruction of the common duct by a plug of mucus or, rarely, a portion of a membranous cast of the gallbladder. Although the majority of earlier observers stated that jaundice occurred only infrequently in patients with noncalculous cholecystitis, more recent studies, with the improved methods now available, have served to emphasize the rather high incidence of hyperbilirubinemia in this condition.

In a series of 375 patients with noncalculous cholecystitis, Hartman [4] found jaundice in 60 cases, or 16 per cent, as compared with 31.74 per cent of a series of 652 patients with gallstones. Kelly and Lyon [5] stated that jaundice may occur in 35.3 per cent of cases of cholecystitis in the absence of gallstones. The latter figure is considerably higher than that given by the majority of authors, but I believe that careful and repeated study of the serum bilirubin concentration will reveal a remarkably high incidence of hyperbilirubinemia, with or without visible jaundice, in patients with acute or chronic cholecystitis which is apparently, although not actually, uncomplicated. In the present series, hyper-

4. Hartman, H. R.: Jaundice in Surgical Cholecystitis Without Stones, M. Clin. North America **7**:89, 1923.

5. Kelly, A. O. J., and Lyon, B. B. V., in Osler and McCrae: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1926, vol. 3, p. 862.

bilirubinemia was present in 16.3 per cent of cases of acute, and in 15.2 per cent of cases of chronic, noncalculous cholecystitis.

Hepatitis, or intrahepatic cholangitis, is perhaps the most common cause of nonobstructive hyperbilirubinemia in patients with cholecystitis. The frequency of occurrence of this lesion is illustrated by the fact that Graham [6] found enlargement of the liver in 25 (83 per cent) of 30 consecutive cases of disease of the biliary tract, evidence of previous or present disease other than enlargement being noted in the remainder. He stated that microscopic evidence of hepatic inflammation, chiefly pericholangitis, may be observed constantly in acute and subacute cholecystitis. Graham's interpretation of these observations has recently been challenged by Noble,[7] who found similar changes almost constantly in livers examined post mortem. Noble stated that portal infiltration by lymphocytes and polymorphonuclear leukocytes seems to have no particular relation to a specific type of disease. He also stated, however, that since no cases of clinical cholecystitis were included in his series, no definite conclusion can be drawn concerning the degree of hepatic inflammation in clinical cholecystitis. This concept of the association between cholecystitis and hepatitis has been supported by the majority of investigators of this problem, including Judd,[8] Deaver,[9] Peterman, Priest and Graham,[10] Moynihan [11] and Tietze and Winkler.[12] It is believed that whereas the hepatic lesion may be and unquestionably is in many instances secondary to the inflammatory process in the gallbladder, in many cases cholecystitis represents a direct extension of the process to the wall of the gallbladder from an already inflamed liver. In either event the extension occurs by way of the lymphatics.

In some cases, the hyperbilirubinemia is undoubtedly obstructive and is due to some obstruction of the free flow of bile through the common duct. In 6 of 7 cases of noncalculous cholecystitis reported by Eusterman,[13] with an average serum bilirubin concentration of 8.1 mg., there

6. Graham, E. A.: Hepatitis; a Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521, 1918.

7. Noble, J. F.: The Relation of Hepatitis to Cholecystitis, Am. J. Path. **9**: 473, 1933.

8. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197 (July 16) 1921.

9. Deaver, J. B.: The Sequelae of Biliary Tract Infection, J. A. M. A. **95**:1641, 1930.

10. Peterman, M. G.: Priest, W. S., Jr., and Graham, E. A.: Association of Hepatitis with Experimental Cholecystitis, Arch. Surg. **2**:92 (Jan.) 1921.

11. Moynihan, B.: Mitchel Banks Memorial Lecture on the Gallbladder and Its Infections, Brit. M. J. **1**:1, 1928.

12. Tietze, A., and Winkler, K.: Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, Arch. f. klin. Chir. **129**:1, 1924.

13. Eusterman, G. B.: Errors in the Diagnosis of Diseases Associated with Jaundice, Ann. Int. Med. **6**:608, 1932.

was definite evidence of associated disease of the liver, pancreas or common duct. Hartman [4] reported the presence of pancreatitis in 26 per cent of 60 patients with jaundice associated with noncalculous cholecystitis. Diamond [14] obtained increased serum bilirubin values in 27 of 98 cases of cholecystitis, the highest being observed in acute cholecystitis (to 12 mg.). Judd, Nickel and Wellbrock [15] stated that hepatitis or cholangitis always occurred in the presence of cholecystitis; the importance of this association was emphasized by Judd and McIndoe,[16] who stated that chronic cholangitis forms the etiologic basis of most microscopic lesions of the liver associated with infection of the gallbladder, and that this infection is more important than obstruction in producing severe hepatic injury. Riedel [17] and Naunyn [18] emphasized the part played by cholangitis and spasm of the common duct in the production of jaundice in disease of the gallbladder. Hyperbilirubinemia in acute forms of cholecystitis is more likely to be due to cholangitis or hepatitis and less likely to be dependent on pancreatitis than in chronic disease of the gallbladder; it occurs more frequently in the more severe than in the mild forms of acute cholecystitis, chiefly because of the higher incidence of hepatitis and cholangitis in the severe cases.

The statement is frequently made that, except in portal cirrhosis, abnormal retention of bromsulphalein occurs only in the presence of hyperbilirubinemia. On the basis of my observations in a large number of patients with noncalculous cholecystitis, I am convinced that the chief practical significance of the bromsulphalein test in such cases lies in the fact that abnormal findings are obtained in a not inconsiderable proportion of patients with acute and chronic cholecystitis without other demonstrable evidence of disturbed hepatic function. This opinion was stated in a previous report [1] and has been strengthened by the data included in the present study. I believe that the presence of retention of bromsulphalein of from 5 to 100 per cent in a group of 32 patients without hyperbilirubinemia is of extreme practical importance. In my previous study there were 3 patients presenting 100 per cent retention of dye with icterus index values of 8.3, 7.2 and 8.7, respectively. In the present group of patients with noncalculous cholecystitis, similar cases were observed: serum bilirubin, 0.83 mg., and retention of dye, 80 per cent (table 2; case 2); serum bilirubin, 0.8 mg., and retention of dye, 100 per cent (case 11); serum bilirubin, 1.1 mg., and retention of

14. Diamond, J. S.: The Value of Routine Estimations of Blood Bilirubin, Am. J. M. Sc. **176**:321, 1928.

15. Judd, E. S.; Nickel, A. C., and Wellbrock, W. L. A.: The Association of the Liver in Disease of the Biliary Tract, Surg., Gynec. & Obst. **54**:13, 1932.

16. Judd, E. S., and McIndoe, A. H.: Cholangitis, J. Michigan State M. Soc. **29**:174, 1930.

17. Riedel: Ueber die Gallensteine, Berl. klin. Wchnschr. **38**:1, 40 and 78, 1901.

18. Naunyn, B.: Cholelithiasis, Tr. New Syndenham Soc., 1896, p. 76.

dye, 100 per cent (table 3; case 16). Such data appear to indicate that in certain cases with only slight if any impairment in the function of excreting bilirubin the capacity of the liver for eliminating bromsulphalein is greatly impaired. These findings suggest dissociation of these two phases of the excretory function of the liver. Such marked grades of retention of dye must be dependent on a widespread disturbance, involving a considerable portion of the liver; on the other hand, this disturbance is apparently readily amenable to correction, since essentially normal findings may be obtained within a short space of time following the institution of proper therapeutic procedures (table 2; case 11). These observations suggest that the hepatic disorder is largely functional, secondary to organic disease of the gallbladder or bile ducts and associated with only slight if any organic disease of the hepatic polygonal cells. The presence of hepatic functional impairment in this group of patients is further evidenced by the observation of hypocholesteremia in 19 and urobilinuria in 20 cases. The significance of hypocholesteremia in this connection has been emphasized by Epstein.[19]

Cholelithiasis.—It is obvious that stones in the gallbladder are not in themselves capable of producing jaundice. However, as has been indicated earlier, disease of the gallbladder is frequently complicated by lesions which may cause hyperbilirubinemia. Hartman [4] found such lesions as hepatic cirrhosis, hepatitis, cholangitis, pancreatitis and mucous plugs in the common duct in a series of 166 patients with jaundice associated with stones in the gallbladder and not in the common duct. Hepatitis was present in 16.9 per cent, cirrhosis in 5.31 per cent, cholangitis in 3.86 per cent, pancreatitis in 28.01 per cent, and enlarged lymph nodes around the bile ducts in 15.45 per cent. Hartman stated the belief that pancreatitis is a common cause of jaundice in such cases. Eusterman [13] reported 85 cases of stones in the gallbladder with jaundice at the time they came under observation, the average serum bilirubin concentration being 7 mg. He stated that gross evidence of changes in the liver, pancreas and extrahepatic bile ducts was noted at operation in 77 per cent of these cases. According to Riedel,[17] extension of spasm or inflammation from the cystic to the common duct is responsible for the occurrence of icterus in from 10 to 15 per cent, and, according to Naunyn,[18] in 40 per cent of cases in which a stone is implanted at the neck of the gallbladder or in the cystic duct.

In the present series of 138 patients with calculous cholecystitis, hyperbilirubinemia was present in 36.2 per cent of cases. Some degree of retention of bromsulphalein was present at some time in 37.6 per cent of these patients. As in the group of persons with noncalculous

19. Epstein, E. Z.: Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, Arch. Int. Med. **50**:203 (Aug.) 1932.

cholecystitis, a marked disproportion between the degree of retention of bromsulphalein and of bilirubinemia was noted in several instances. This, with the not infrequent occurrence of hypocholesteremia and urobilinuria, is in my opinion highly suggestive of the fact that hepatic functional impairment is a not uncommon complication of calculous cholecystitis in the absence of clinical jaundice or, at times, hyperbilirubinemia. The aforementioned statements in connection with noncalculous cholecystitis are equally applicable here.

Naturally, because of the possibility of effectively obstructing the outflow of bile, stones in the common duct are more likely to produce hyperbilirubinemia than are stones in other portions of the bile passages. According to Kehr,[20] about 75 per cent of all patients with stones in the common bile duct have jaundice at some time. In a series of 1,608 cases, Judd and Marshall [21] obtained a history of jaundice in 73.4 per cent, icterus being present at the time of admission in 18.8 per cent of the patients. Jordan [22] and Weir [23] stated that about 13 per cent of persons with stone in the common bile duct exhibited no jaundice at any time. Moynihan [24] stated that jaundice is absent in 25 per cent of these cases. Some degree of cholangitis, hepatitis, cholecystitis and pancreatitis is commonly present in association with stone in the common duct. Kehr [20] and Riedel [17] minimized the mechanical rôle of the stone and emphasized the inflammatory reaction in the duct mucosa as the cause of jaundice, Riedel stating that the latter factor is operative in 40 per cent of cases.

Hyperbilirubinemia was present in 81 per cent of 37 patients in this series with stone in the common duct. Some degree of retention of dye was present in 75.6 per cent of these cases. Obviously, little if any information can be gained from studies of the retention of bromsulphalein during periods of obstructive jaundice. However, as may be noted in cases 2, 3 and 6 (table 7), the speed of restoration of the capacity of the liver for eliminating bromsulphalein does not always parallel the decrease in the degree of bilirubinemia which follows spontaneous resumption of the flow of bile. Case 4 illustrates the existence of marked retention of dye in the absence of hyperbilirubinemia.

It has been my experience, as is illustrated by several cases included in this report, that the routine study of the state of hepatic function

20. Kehr, H.: Chirurgie der Gallenwege, Berlin, Ferdinand Enke, 1913.

21. Judd, E. S., and Marshall, J. M.: Gallstones in the Common Bile Duct, Arch. Surg. **23**:175 (Aug.) 1931.

22. Jordan, F. M.: Stones in the Common Bile Duct Without Jaundice, Proc. Staff Meet., Mayo Clin. **5**:56, 1930.

23. Weir, J. F.: Diagnosis of Jaundice: Value of Clinical and Laboratory Data, Am. J. Surg. **15**:494, 1932.

24. Moynihan, B.: The Correlation of Symptoms and Signs in Some Abdominal Diseases, Brit. M. J. **1**:345, 1912.

in all patients with calculous and noncalculous cholecystitis, so far as it can be studied, frequently yields information of distinct practical value. The presence of retention of bromsulphalein is particularly significant in the absence of or during the disappearance of obstructive jaundice. On the basis of the data presented, three points deserve special emphasis; (1) that some evidence of disturbed hepatic function can be obtained in a fairly large proportion of cases of calculous and noncalculous cholecystitis; (2) that marked grades of retention of bromsulphalein may occur in patients with disease of the biliary tract in the absence of hyperbilirubinemia; (3) that in certain cases of stone in the common duct, some degree of retention of dye persists for a variable period after a previously high serum bilirubin concentration has returned to normal. In my opinion, appreciation of these facts will do much to diminish the postoperative morbidity and mortality of operations on the biliary tract.

SUMMARY

1. In a group of 49 patients with acute cholecystitis, hyperbilirubinemia was present at some time in 8 cases, retention of bromsulphalein in 11, hypercholesteremia in 2, hypocholesteremia in 4, and urobilinuria in 4.

2. Some evidence suggestive of hepatic functional impairment was noted in 76 (26.3 per cent) of 288 patients with chronic noncalculous cholecystitis. Retention of bromsulphalein without hyperbilirubinemia was noted in 32 cases, hyperbilirubinemia and retention of dye in 29 and hyperbilirubinemia without retention of dye in 15. Hypercholesteremia was present in 4 cases, hypocholesteremia in 15 and urobilinuria in 16.

3. Evidence suggestive of hepatic functional impairment was obtained in 61 (44.8 per cent) of 138 patients with calculous cholecystitis. Retention of dye was present in 52 cases, hyperbilirubinemia in 50, hypercholesteremia in 7, hypocholesteremia in 15 and urobilinuria in 15.

4. Abnormal findings were obtained in 31 (83.7 per cent) of 37 patients with stone in the common bile duct. In some cases it was noted that the speed of restoration of the capacity of the liver for eliminating bromsulphalein did not parallel the decrease in the degree of bilirubinemia which follows spontaneous resumption of the flow of bile.

5. The data reported illustrate the frequency of occurrence of hepatic functional impairment in apparently uncomplicated disease of the gallbladder. Retention of bromsulphalein of marked degree may exist in the absence of hyperbilirubinemia.

PUTRID EMPYEMA

WITH SPECIAL REFERENCE TO ANAEROBIC STREPTOCOCCI

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Cases of abscess of the lung, pulmonary gangrene, bronchiestasis and certain types of bronchopneumonia are occasionally complicated by the development of pleural effusion. When the pleural fluid is aspirated, it is frequently found to be purulent and to have a foul odor. It is because of this characteristic odor that a pleural effusion of this type is termed putrid empyema. Occasionally this fluid is thin, but more often it is moderately thick and of creamy consistency. It may be yellowish-green or brown, depending on the amount of fresh or changed blood present. In spite of the fact that microscopic examination of the putrid exudates often reveals the presence of many micro-organisms, attempts to cultivate the bacteria under ordinary aerobic conditions may prove unsuccessful. However, the use of anaerobiasis often yields an abundant growth of one or more kinds of bacteria.

The purpose of this article is to report the bacteriologic observations and clinical course in 7 cases of severe purulent infections and to emphasize the occurrence and probable importance of anaerobic streptococci in the pathogenesis of the diseases from which the patients suffered. Four of the patients had putrid empyema, 2 had pulmonary abscess, and 1 had multiple hepatic abscesses. The cases of empyema were studied in more detail than the others. Consequently, the clinical and bacteriologic observations of these cases are given special consideration in this communication.

REVIEW OF THE LITERATURE

A review of the literature dealing with putrid, purulent infections reveals a diversity and complexity of bacteriologic results, and each author stresses the importance of a different organism or combination of organisms. The association of anaerobes, including anaerobic streptococci, with putrid empyema has been recognized for many years, and organisms of similar types are also found in various other pathologic states, such as pulmonary abscess and gangrene, puerperal infections

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and mastoiditis. An attempt is made here to summarize the literature dealing with putrid empyema and also that dealing with infections in which the anaerobic streptococcus is found. Thus it may be possible to throw some light on the significance of this type of organism and to gain some insight into its importance in certain infections.

Lesions in Which Anaerobic Streptococci Are Found.—The occurrence of an anaerobic streptococcus in pathologic lesions was first mentioned by Veillon,[1] in 1893, who isolated it from a case of bartholinitis. The pus had a foul odor, as did the culture of the coccus and the pus from an abscess produced by subcutaneous injection of the organism into an animal. Veillon also found the organism in the fetid pus from a case of Ludwig's angina and from a perinephric abscess, but in the latter cases it was in association with a pyogenic streptococcus. Two years later Krönig [2] described the occurrence of an anaerobic streptococcus, sometimes alone and sometimes with anaerobic bacilli, in the vaginal secretion during pregnancy. The streptococcus was found to be avirulent for rabbits. Since the reports of these earlier workers, the studies of many authors up to the present time have indicated the widespread occurrence of the anaerobic streptococcus in many and varied lesions. A review of the literature shows that it may be found under a great variety of conditions, but the two types of infections in which it seems to play its most important rôles are: (1) putrid or gangrenous lesions of the lung or pleura and (2) puerperal infections with or without sepsis.

In Putrid Empyemas (and Pulmonary Lesions): The majority of the authors who have studied the subject of putrid pleurisy have found that the pus from these lesions contains an anaerobic streptococcus. This organism is nearly always associated with other bacteria, however, especially with anaerobic bacilli, fusiform bacilli and spirochetes. In 1899, anaerobic streptococci and gram-negative bacilli were found by Rendu and Rist [3] in 3 cases of putrid pleurisy. Guillemot, Hallé and Rist [4] found the organism (as well as anaerobic bacilli and aerobic streptococci) in the majority of 13 cases of putrid empyema. In 1921,

1. Veillon, A.: Sur unmicrocoque anaérobe trouvé dans des suppurations fétides, Compt. rend. Soc. de biol. **5**:807, 1893.

2. Krönig: Ueber die Natur der Scheidenkeime, speciell über das Vorkommen anaërober Streptokokken im Scheidensekret Schwangerer, Centralbl. f. Gynäk. **19**: 409, 1895.

3. Rendu and Rist, E.: Etude clinique et bactériologique de trois cas de pleurésie putride, Bull. et mém. Soc. méd. d. hôp. de Paris **16**:133, 1899.

4. Guillemot, L.: Hallé, J., and Rist, E.: Recherches bactériologiques et expérimentales sur les pleurésies putrides, Arch. de méd. expér. et d'anat. path. **16**:57 and 677, 1904.

Bingold [5] stressed the formation of gangrenous or fetid pulmonary and pleural lesions as a result of emboli containing the anaerobic streptococcus lodging in the lungs in the course of thrombophlebitic puerperal sepsis. In these cases the organism can be obtained from the pelvic veins, the blood stream and the pulmonary lesions. Bingold concluded that the chief cause of embolic pulmonary gangrene is the anaerobic streptococcus. Davis and Pilot [6] found it with a fusiform bacillus and spirochete in 4 cases of putrid pneumonia and were able to culture it and the fusiform bacillus from the empyema fluid which developed in 1 of the cases. Similar bacteriologic observations were reported by Leckie [7] in 1 case of putrid empyema. Eggers [8] found streptococci, some of which were apparently anaerobic, in several cases of empyema secondary to pulmonary abscesses. Anaerobic cocci, bacilli and spirochetes were found in the putrid pleural fluid of a patient by Bezançon and his co-workers [9] and later in another case by Jacquelin, Brun and Fouquet.[10] Brown [11] and Colebrook,[12] who were studying the relation of the anaerobic streptococcus to puerperal infection each had a case in which it could be grown from the pleural fluid as well as from the blood. Pilot [13] reported a case of putrid empyema in which streptococci and fusiform bacilli were found in the stained smear of the fluid, while culture revealed only an anaerobic streptococcus.

A summary of the bacteriologic reports on approximately 26 cases of putrid empyema collected from the literature shows that the anaerobic streptococcus was found in 13 (probably also in 4 others in which strep-

5. Bingold, K.: Putride embolische Lungeninfektionen; Aetiologie und Pathologie, Virchows Arch. f. path. Anat. **232**:22, 1921; Die Bedeutung anaërober Bacterien als Infektionserreger septischer interner Erkrankungen, ibid. **234**:333, 1921.

6. Davis, D. J., and Pilot, I.: Studies of Bacillus Fusiformis and Vincent's Spirochete, Habitat and Distribution of these Organisms in Relation to Putrid and Gangrenous Processes, J. A. M. A. **79**:944 (Sept. 16) 1922.

7. Leckie, J. P.: Fatal Case of Empyema Due to Anaerobic Infection, Edinburgh M. J. **30**:60 (Feb.) 1923.

8. Eggers, C.: Lung Abscess Complicated and Hidden by Empyema, Arch. Surg. **12**:338 (Jan.) 1926.

9. Bezançon, F., and others: Sur la présence de spirochaetes associés aux anaerobes dans un cas de pleurésie putride, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1153 (July 14) 1927.

10. Jacquelin, A.; Brun, C., and Fouquet: Sur un cas de pleurésie putride causé par la flore spirochéto-anaérobe, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1219 (Nov.) 1929.

11. Brown, T. K.: The Incidence of Puerperal Infection Due to Anaerobic Streptococci, Am. J. Obst. & Gynec. **20**:300 (Sept.) 1930.

12. Colebrook, L.: Infection by Anaerobic Streptococci in Puerperal Fever, Brit. M. J. **2**:134 (July 26) 1930.

13. Pilot, I.: Putrid Empyema as a Postoperative Complication, M. Clin. North America **13**:1227 (March) 1930.

tococci were found in a smear of the fluid, although no growth was obtained), gram-negative bacilli in 5 or 6, gram-positive bacilli in at least 2, fusiform bacilli in 5, spirochetes in 5, anaerobic staphylococci in 4, aerobic Staphylococcus aureus in 1 and aerobic streptococci in 2. This summary by no means contains all of the cases of putrid pleurisy which have been reported, but in others the bacteriologic studies are not so definite as the aforementioned, and these give a general idea of the organisms most often found.

Inasmuch as putrid empyemas are rarely, if ever, primary but practically always secondary to intrapulmonary suppuration or necrosis, it is not surprising that the anaerobic streptococcus is being found frequently in the primary or pulmonary as well as in the secondary or pleural lesions. Various authors have cultured the anaerobic streptococci from putrid pulmonary infections such as abscess, gangrene and bronchiectasis. The observations of Bingold have been mentioned earlier; Lehmann, too, pointed out the nearly constant occurrence of putrid lung pulmonary abscesses in the course of puerperal sepsis due to the anaerobic streptococcus. In addition, there are the reports of Davis and Pilot,[14] who found a streptococcus which was "often anaerobic in early cultures," in cases of putrid pneumonia, pulmonary abscess and gangrene (in association with spirochetes and fusiform bacilli); Lambert and Miller [15] grew it from 6 of 10 cases of pulmonary abscess (an anaerobic gram-negative bacillus was found in 7); Smith [16] found only anaerobes in the pus from 3 cases of pulmonary abscess—cocci, vibrios, fusiform bacilli and spirochetes—and the same organisms were shown in sections of the ulcerated bronchi in acute cases. Ermatinger [17] isolated facultatively anaerobic streptococci in some cases of pulmonary abscess and bronchiectasis. Cohen [18] cultured an anaerobic streptococcus from the pus in each of 16 cases of pulmonary abscess; in all of these there was also a diphtheroid bacillus, and in 14 of the 16 there was a strictly anaerobic gram-negative bacillus (Bacillus melaninogenicum, an organism producing black pigment and a fetid odor on blood agar). The streptococcus was nonhemolytic and was called a "doubtful" anaerobe

14. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochetes: Their Rôle in Pulmonary Abscess, Gangrene and Bronchiectasis, Arch. Int. Med. **34**:313 (Sept.) 1924. Davis and Pilot [6]

15. Lambert, A. V. S., and Miller, J. A.: Abscess of Lung, Arch. Surg. **8**: 446 (Jan.) 1924.

16. Smith, D. T.: Fuso-Spirochetal Disease of the Lungs, Tubercle **9**:420 (Nov.) 1927.

17. Ermatinger, L. H.: Micro-Organisms of Lung Abscess and Bronchiectasis, J. Infect. Dis. **43**:391 (Nov.) 1928.

18. Cohen, J.: Bacteriology of Abscess of Lung and Methods for Its Study, Arch. Surg. **24**:171 (Feb.) 1932.

because it was found to grow aerobically on subcultures though not on the original one.

In Puerperal and Pelvic Infections: In 1910 Schottmüller [19] found the anaerobic streptococcus in 17 cases of septic abortion; in 5 he obtained it in pure culture from the blood. (He also cultured it in 2 cases of otitis media and in 1 case of pulmonary gangrene.) In cases of puerperal sepsis or septic abortion due to this organism, these infections are usually associated with pelvic thrombophlebitis, and Schottmüller stated the belief that the streptococci are able to "dissolve the thrombi" so that small particles break off. In 1924 [20] he cultured the anaerobic streptococcus from the blood and peritoneal exudate during life in 39 of 230 fatal cases of sepsis following labor. Many other authors have shown the importance of this organism in puerperal infection, and their studies indicate that it is not only commonly found under these conditions, but that its pathogenicity is comparable to that of the aerobic hemolytic streptococcus. Bingold [5] discussed the importance of the anaerobic streptococcus in various infections, especially in puerperal fever with thrombophlebitis. He had seen 60 cases of sepsis due to this organism, in all of which pulmonary abscess or gangrene developed; he stated that the fatal outcome of cases of sepsis due to an anaerobic streptococcus is often due to the pulmonary complications. Three of the patients had purulent meningitis, and 3 had endocarditis. Lehmann [21] also reported 3 cases of endocarditis due to this streptococcus, associated with septic abortion and bacteremia. (In neither of these cases was there a history of previous rheumatism or of old endocarditis histologically.) Lehmann found it to be the single infecting agent in 17 of 27 cases of sepsis with thrombophlebitis, in 8 of 12 cases of pelvic abscess and in many cases of salpingitis. Schwarz and Dieckmann [22] cultured the streptococcus from the blood in 30 of 123 cases of puerperal infection, and later [23] from the blood in 10 of 45 cases. Harris and Brown [24] found it with approximately the same frequency as the aerobic

19. Schottmüller, H.: Zur Bedeutung einiger Anaëroben in der Pathologie insbesondere bei puerperalen Erkrankungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **21**:450, 1910.

20. Schottmüller, H.: Ueber die Artverschiedenheit der Streptokokken, München. med. Wchnschr. **71**:1009, 1924.

21. Lehmann, W.: Die Bedeutung anaërober Streptokokken für die Aetologie der akuten septischen Endokarditis, München. med. Wchnschr. **73**:233, 1926.

22. Schwarz, O. H., and Dieckmann, W. J.: Anaerobic Streptococci: Their Rôle in Puerperal Infection, South. M. J. **19**:470 (June) 1926.

23. Schwarz, O. H., and Dieckmann, W. J.: Puerperal Infection Due to Anaerobic Streptococci, Am. J. Obst. & Gynec. **13**:467, 1927.

24. Harris, J. W., and Brown, J. H.: A Clinical and Bacteriological Study of 113 Cases of Streptococcic Puerperal Infection, Bull. Johns Hopkins Hosp. **44**:1 (Jan.) 1929.

hemolytic streptococcus in 113 cases of puerperal infection. The majority of these streptococci were of the gamma nonhemolytic variety, and many of them failed to ferment the test sugars. Brown [11] found that this streptococcus was the infecting agent in a little more than half of 203 cases of puerperal infection. Colebrook [12] isolated the anaerobic streptococcus from the blood of 17 patients with puerperal fever, 7 of whom died and 1 of whom had "terminal" endocarditis.

The anaerobic streptococcus is also found in many other pathologic processes throughout the body, as may be shown by a glance at the literature. In 1898 Veillon and Zuber [25] found it in cases of gangrenous appendicitis and in a case of mastoiditis with pulmonary gangrene. In 1905 Rist [26] reported its isolation from cases of appendicitis, puerperal infection, bartholinitis, infection of the urinary tract, otitis media and mastoiditis. Lehmann [21] stated that the organism sometimes produces foul-smelling tonsillar abscesses, and that it may be found in cases of appendicitis, frequently in mixed infections of the deep portion of the bronchial tree, in diseases of the ear, and in Vincent's angina, putrid alveolar abscesses and the like.

A classification of the strains of this streptococcus was given by Prévot [27] in 1925. He described six strains: 1. Micrococcus foetidus (Veillon, 1893), a strict anaerobe, produces gas and a foul odor and ferments saccharose but not lactose, maltose or mannite. 2. Streptococcus anaerobicus (Krönig, 1895; Natvig, 1905) is found especially in puerperal sepsis and is a strict anaerobe. One strain ferments saccharose and maltose; the other, maltose and mannite, producing gas and odor. 3. Streptococcus putridus (Schottmüller), a strict anaerobe, produces gas and odor. Maltose is fermented and occasionally saccharose and mannite. 4. Streptococcus anaerobius-micros (Lewkowicz, 1901) produces no gas or odor and no coagulation of milk or fermentation of saccharose and maltose. 5. Streptococcus intermedius, a strict anaerobe, is found in pulmonary conditions. It forms gas with a foul odor, coagulates milk with the production of acid and ferments maltose, lactose and, occasionally, saccharose. 6. Streptococci which are "anaerobes by predilection" show growth in the air, though it is slow and poor. Fourteen strains are reported, eleven of which are from pulmonary conditions. At first the organism is a strict anaerobe, but later it grows also aerobically, though not nearly so well. Gas and a foul odor are not produced in culture mediums. Milk is coagulated and acidified. Saccharose, mal-

25. Veillon and Zuber: Recherches sur quelques microbes strictement anaérobes et leur rôle en pathologie, Arch. de méd. exper. et d'anat. path. **10**:517, 1898.

26. Rist, E.: Anaérobes pathogènes et suppurations gangréneuses, Bull. Inst. Pasteur **3**:1 and 49, 1905.

27. Prévot, A. R.: Les streptocoques anaérobes, Ann. Inst. Pasteur **39**:417, 1925.

tose and lactose are fermented. Prévot called this streptococcus Streptococcus evolutus. (He remarked that these anaerobic streptococci "live as saprophytes in the natural cavities and can become pathogenic when the opportunity offers".)

Pathogenicity for Animals.—From the review of the literature just presented, it is evident that the majority of the reports dealing with the anaerobic streptococcus lead one to the conclusion that, at least under certain conditions, it is a truly pathogenic organism, in spite of the fact that it is frequently spoken of as a saprophyte of minor importance. The reports of experimental studies with this streptococcus are not extensive, and though some investigators show that it is pathogenic for animals when in association with other anaerobes, few have shown that pure cultures of the organism are capable of producing lesions in animals. Veillon [1] produced foul-smelling, subcutaneous abscesses with cultures of an anaerobic streptococcus (M. foetidus). The anaerobes isolated by Guillemot and his co-workers [4] (M. foetidus, Staphylococcus parvulus, Bacillus ramosus and others) caused putrid lesions in rabbits and guinea-pigs when the original pus was injected. In this way, putrid pleurisy could be passed on from animal to animal, but none of the bacteria in pure culture were pathogenic. In 1905 Rist [26] found that anaerobes (bacilli and cocci) which he had isolated from various putrid lesions were pathogenic for animals when injected subcutaneously, intrapleurally or intracutaneously. Pilot and Davis [14] produced putrid empyemas in rabbits by intrapleural injections of tooth scrapings and tonsillar débris. The material that was injected, as well as the pus from the pleural cavity, contained spirochetes, fusiform bacilli and cocci. The cocci, when injected in pure culture, produced serofibrinopurulent pleuritis but no odor. In 1930 Smith [28] showed that putrid pulmonary infections or subcutaneous abscess could be produced in rabbits by intratracheal or subcutaneous injections of mixtures of pure cultures of Treponema microdentium, a small fusiform bacillus, a vibrio and an anaerobic hemolytic streptococcus. No strain by itself and no other combination could form lesions.

Some authors have definitely stated that they did not find the anaerobic streptococcus pathogenic for animals (Krönig,[2] Guillemot and others,[4] Schottmüller [19] and Lehmann [21]). Schottmüller employed cultures of an anaerobic streptococcus isolated from cases of pelvic infection and injected them into rabbits and guinea-pigs without producing any ill effects. The rabbits received intravenous, intramuscular and subcutaneous injections, and the guinea-pigs, intraperitoneal and subcutaneous injections. Cohen [18] found that the doubtful anaerobic strep-

28. Smith, D. T.: Fusospirochetal Disease of the Lung Produced with Cultures from Vincent's Angina, J. Infect. Dis. **46**:303 (April) 1930.

tococcus which he obtained from pulmonary abscesses was not pathogenic for rabbits or guinea-pigs after intravenous or intracutaneous inoculation.

Summary.—Thus from the literature one gathers that the anaerobic streptococcus is an organism which may be found in a variety of pathologic conditions—especially those of a putrid or gangrenous nature—throughout the body. The lesions in which it seems to play its most important rôles are suppurations in the lung or pleural cavity and puerperal or other pelvic infections. The evidence points to the fact that it is definitely pathogenic for man; this is particularly convincing in cases of puerperal sepsis, when it can be obtained in pure culture from the pelvic veins, the blood and pulmonary abscesses; in these cases it likewise occasionally produces endocarditis. The experimental work is not conclusive; two authors obtained lesions in animals with this organism, while others have found that pure cultures of the anaerobic streptococcus are avirulent for animals, whereas with cultures in combination with other anaerobes the lesions can often be produced.

REPORT OF CASES

The 4 cases of putrid empyema included in this report were associated with an anaerobic streptococcic infection. In 1 case, which will be reported in detail, the organism (an anaerobic streptococcus) was the principal factor in the production of the patient's pneumonia, with resultant pulmonary abscess, empyema, metastatic abscesses in the skin and bones, endocarditis and eventual death. In 3 other cases it was the most conspicuous organism present, although associated with other anaerobes. In 2 cases it was obtained from pulmonary abscesses at operation. In 1 rather obscure case of unexplained fever it was responsible for the production of multiple hepatic abscesses.

CASE 1.—*History.*—F. B., aged 26, a colored laborer, married, was admitted to the hospital on Jan. 20, 1932, and died on March 14. The chief complaints were sore throat and great weakness of two weeks' duration. The family history was noncontributory. The general health had been good. The patient had had a primary syphilitic lesion five years before admission, which was inadequately treated by his family physician. For eight or ten years he had been troubled with an occasional dry cough and infrequent sweats at night; there had been no thoracic pain, dyspnea or hemoptyses. The patient had done the heavy work of a laborer prior to his admission to the hospital.

Sixteen days before admission he caught a cold following exposure to wet weather. Three days later a sore throat with pain on swallowing developed. Two days later the patient came to the hospital, where his temperature was found to be 101.6 F.; the tonsils were red and covered with exudate. He was given sodium perborate as a gargle. He reported in the outpatient department the next day. The throat appeared to be unchanged, but the temperature had risen to 102 F., accompanied by a chill. He was advised to go home to bed and force fluids.

The Wassermann reaction was strongly positive. He returned to the outpatient department four days later, feeling much weaker and sick. During the next five days at home he became much worse; he was hoarse and had several chills followed by profuse sweats. One week prior to admission, he had a cough and blood-streaked sputum. He grew short of breath, and noticed pain in the left shoulder and right buttock. A sharp pain across the front of his chest when he coughed brought him into the hospital.

Physical Examination.—The temperature was 103.8 F., the pulse rate, 140; the respirations, 42, and the blood pressure, 106 systolic and 64 diastolic. The positive findings were as follows: The patient was an emaciated, acutely ill colored man. The skin was hot and moist, and the forehead covered with perspiration. The conjunctivae were pale. The pupils were irregular and reacted sluggishly to light. Examination of the throat and mouth showed that the tongue was heavily coated; there was much sordes over the lips; pyorrhea was marked and the tonsils were enlarged and covered with exudate. The voice was hoarse. The trachea was in the midline. Respirations were shallow and rapid. There was dulness in the right axilla and interscapular region, with marked suppression of the breath sounds and many moist râles. Bronchovesicular breathing was heard in the right posterior axillary line. The left lung was clear. The heart was not enlarged. It was thought to be slightly displaced to the left. The rate was rapid and regular. The sounds were of good quality. No murmurs were heard. The peripheral vessels seemed normal, and the pulse was of good quality. The abdomen was somewhat distended but not tender. The liver and spleen were not felt. There was neither clubbing of the fingers nor edema of the extremities. The patient complained of pain in the right hip, but examination did not disclose any cause for this. There was tenderness about the left shoulder joint with pain on motion, but no swelling.

Examination of the Blood.—The red blood cells numbered 3,300,000. The hemoglobin was 72 per cent, and the white cells 16,000, with 90 per cent polymorphonuclear leukocytes. The red cells were slightly pale; the platelets were normal in number. The urine showed: specific gravity, 1.020; albumin, 2 plus; sugar, 0; many granular casts, white blood cells and occasional red blood cells. Culture of the throat produced Staphylococcus aureus and diphtheroids.

Course in the Hospital.—The physical signs in the chest were suggestive of a pleural effusion, and thoracentesis was done on the evening of admission. The needle was inserted in several places over the right lower region of the chest posteriorly, in the region of the midaxillary line. Seventy-five cubic centimeters of fluid was withdrawn. It was foul-smelling, thin and reddish brown. A smear of the fluid showed a predominance of gram-positive cocci, mixed with gram-negative bacilli, fusiform bacilli and spirochetes. A smear from the throat showed a few spirochetes. The empyema was thought to have resulted from the rupture of a pulmonary abscess. The temperature rose to 105.6 F., and the condition became worse. A thoracotomy was done that night, and a trocar inserted in the seventh interspace in the midaxillary line. A rubber catheter was left in place and drainage instituted by means of continuous tidal irrigation (described by Hart). One hundred cubic centimeters of brownish foul pus was evacuated at the time of operation.

A blood culture taken on admission showed no growth aerobically. However, an anaerobic streptococcus was grown on cooked meat medium under a seal.

The patient was given fluids by mouth and subcutaneously in the thigh. Following a transfusion the next day he showed definite improvement. During the next

week the temperature varied between 101 and 105 F., accompanied by profuse sweats. There was a slight cough but no sputum. The patient had frequent chills. On the eighth day after admission the red blood cells had fallen to 2,500,000, and the hemoglobin to 50 per cent. The patient was given another transfusion with temporary improvement. The urine continued to show a moderate amount of albumin, a few red cells and white cells and few casts. Roentgenograms of the chest showed a "small area of partial consolidation in the lower lobe of the right lung." Physical examination revealed only a small amount of fluid in the right side of the chest.

On the tenth day after admission a firm swelling was noticed above the left clavicle at the acromial junction. This was quite tender. No evidence of osteomyelitis could be determined by roentgenograms, but a dense shadow was present in the soft tissues above the left clavicle. This area was treated with compresses. The temperature continued to vary daily from 100 to 104 F., the pulse rate between 110 and 140 and the respirations from 40 to 50. Frequent chills continued. The patient next had tenderness and induration over the right hip, with crepitation on palpation. A roentgenogram showed that there was air in the soft tissues. Blood culture taken on January 28 (the eighth day after admission) again yielded anaerobic streptococci. The signs over the lung changed little. The apparatus for irrigation often became obstructed, and drainage was not free. There were progressive anemia and leukocytosis.

On February 5, fifteen days after admission, a large abscess on the right heel was opened, and 75 cc. of foul-smelling pus was obtained. This pus had the same odor as that obtained from the pleural cavity; smears of this fluid showed only a gram-positive coccus which on culture proved to be the same anaerobic streptococcus. Pus was also obtained from a similar area on the left heel. On the same day an incision was made into the area of swelling about the left clavicle, and 50 cc. of pus of a similar character was obtained. Smears and culture showed the same organism. Sputum was obtained on several occasions. It did not show tubercle bacilli; hemolytic aerobic streptococci predominated. The improvement following the drainage of these areas was only temporary; the next day another abscess on the left buttock was drained, and a large amount of the same foul pus was obtained. Subsequently, the right knee was incised with the same results.

It was noted that each abscess contained much air, as well as thick, creamy, foul-smelling pus. The empyema irrigation system was also continually full of air, suggesting either a bronchial fistula or the production of air by the streptococcus. A roentgenogram of the left clavicle showed osteomyelitis of its outer end. The patient's condition grew progressively worse, in spite of repeated transfusions and apparently adequate drainage from numerous areas of abscess over the body. Repeated examinations of the heart revealed nothing that was not consistent with the anemia. The patient died on March 14, fifty-two days after admission and approximately sixty-six days from the onset of illness.

Autopsy.—Autopsy was performed on March 15, 1932. The anatomic diagnosis was: abscesses in the right lung, bronchial fistulas, organizing pneumonia, organizing fibrinopurulent pleurisy, purulent bronchitis, lobular pneumonia, septicemia (an anaerobic streptococcus), streptococcic endocarditis of the mitral valve, scars in the myocardium, osteomyelitis of the left clavicle, purulent arthritis of the right knee joint, multiple draining subcutaneous sinuses, acute nephritis, hypoplasia of the bone marrow, secondary anemia, hemosiderin in the liver and spleen and a decubitus ulcer.

A summary of the important gross and microscopic pathologic observations follows: The heart valves were thin and delicate, but there were several friable, gray-pink vegetations on the mitral valve. There were several abscess cavities of various sizes in the right lung, which communicated with one another by small openings, one of which extended to the pleural cavity. One cavity in the right lower lobe also communicated with a bronchus and with the operative wound in the chest to produce a bronchial fistula. A fibrinopurulent exudate was found in the right knee joint, with extensive destruction of the cartilage. There was extensive osteomyelitis of the left clavicle. The kidneys showed numerous punctate hemorrhages. The other organs were grossly normal.

Microscopically, one of the large cavities in the lung showed a communication with a bronchus, and the wall of the cavity was lined by granulation tissue, but there were areas suggesting smooth muscle in the wall of the cavity, probably representing a bronchiectatic dilatation of the chronically infected bronchus. However, there were fresh abscesses in the pulmonary substance. In the pleura there was a thick layer of granulation tissue with a more superficial, fresh fibrinopurulent exudate. All of these infections were apparently caused by an anaerobic streptococcus. No spirochetes were found. The vegetations on the mitral valve contained numerous colonies of bacteria; the vegetations were partly organized. The kidneys showed numerous hemorrhages with blood in the tubules. The bone marrow of the femur was gelatinous in appearance, and most of the myeloid cells had disappeared. The rest of the organs were normal.

Laboratory Studies.—The original pleural fluid was thin and reddish brown and had a foul odor. A smear made from the fluid showed spirochetes, fusiform bacilli, many gram-positive cocci and gram-negative bacilli. There was no growth of the first culture aerobically on blood agar or in beef infusion broth. Another culture of the pus on blood agar aerobically showed, after five days, a few fine colonies of cocci which seemed to be just under the surface and were difficult to scrape off. Another sample of the pus put into a broth tube (aerobically) produced a slight granular growth at the bottom of the tube. Cultured anaerobically on cooked meat medium beneath a petrolatum seal, there were a granular growth and the production of gas with a foul odor. A stained smear of this culture showed only gram-positive cocci in short chains, singly and in pairs. A culture of the pleural pus on blood agar in an anaerobe jar showed a growth of small colonies of streptococci with a narrow zone of complete hemolysis. The other bacteria which were seen in smears of this pus grew neither aerobically nor anaerobically. In milk medium under petrolatum there was rapid growth, with the production of much acid, clotting and an offensive odor. In sugar mediums beneath petrolatum there was fermentation of sucrose, dextrose, maltose and lactose, but none of mannite. Anaerobic growth in broth produced only a slight odor. Transfer of the culture from the cooked meat medium to blood agar showed slow, fine growth aerobically after from five to eight days, and in an anaerobe jar on blood agar, good growth in two days with moderately intense but complete hemolysis.

Experiments in Animals (Brooks Strain).—Intrapleural Inoculations: Six rabbits received intrapleural injections with cultures of the anaerobic streptococcus. The details are as follows: One cubic centimeter of a twenty hour culture of the Brooks strain of anaerobic streptococcus grown in a cooked meat medium beneath a petrolatum seal was injected into the right pleural cavity of one rabbit, and 3 cc. into another. The first rabbit died within sixteen days, with massive empyema and abscesses of the mediastinum and of the mesentery. The anaerobic

streptococcus was recovered from the lesions in pure culture; it grew slowly and poorly aerobically but quickly anaerobically. The other animal was killed after six weeks and had a large walled-off empyema, the lung being destroyed on that side. Aerobic culture produced no growth, but there was good growth of the streptococcus under anaerobic conditions.

The cooked meat culture from the empyema in the first rabbit was then injected intrapleurally into another rabbit (3.5 cc.); it resulted in the death of the animal in twelve days and the production of another massive empyema. The lung on that side was a consolidated, necrotic mass. There were also abscesses in the mediastinum and purulent pericarditis. The anaerobic streptococcus was recovered from each lesion in pure culture. Two and five-tenths cubic centimeters of the cooked meat culture from this empyema was then injected into the right pleural cavity of each of two rabbits. One died within five days of empyema, localized abscess between the heart and the diaphragm (this abscess contained gas) and acute fibrinous pericarditis. The other rabbit's chest was aspirated after one month, pus was obtained and the same streptococcus isolated. The animal was killed after two and a half months, when apparently in good condition. A large walled-off empyema was found; the lung on that side was necrotic, and there were some smaller abscesses in the mediastinum. Stained smear of this pus showed streptococci and gram-negative bacilli, but cultures gave no growth aerobically or anaerobically. The sixth rabbit of this series was given 3 cc. of a culture of the streptococcus from the empyema of the fourth rabbit. The animal died within sixteen days, and autopsy showed empyema and abscesses of the mediastinum and of the wall of the chest. The right lung was necrotic.

A summary of the experimental empyemas produced in rabbits therefore shows that in each of 6 rabbits which received intrapleural injections of young (eighteen to twenty-four hour) cultures of the anaerobic streptococcus, massive empyema resulted. The empyema had the same characteristics in each case, except that in the cases of the rabbits surviving for a longer time it was surrounded by a more dense wall, and the pus had a much thicker consistency. Two of the 6 rabbits received injections of the original culture, while the other 4 received injections of cultures passed on from the empyema in the first animal. Each culture had the same characteristics: It was a granular growth in a cooked meat medium under a petrolatum seal; there were a small amount of gas and a moderately foul odor, and stained smears showed only streptococci in short chains. Two of the rabbits survived and were apparently in good condition when killed after six weeks and two and one half months, respectively, but the other four died within from five to sixteen days. The pus in each case was thick and white and did not have a foul odor. In only one case was gas found in any of the abscesses, and that was in an abscess between the heart and diaphragm. In 4 of the 6 cases there were also abscesses in the region of the mediastinum. In 1 there were abscesses in the mesentery. There were purulent pericarditis in 1 animal and fibrinous pericarditis in another.

In 1 rabbit the injection was made by mistake into the liver, and the animal was killed within three days when sick. A large multilocular abscess was found in the liver.

Subcutaneous Inoculations: In 2 rabbits, approximately 0.5 cc. of the culture was injected beneath the skin of the thoracic wall, and a hard, localized abscess was produced with no evidence of redness of the skin over it; the abscesses showed no tendency to progress and were found to contain thick, white pus.

Intracutaneous Inoculations: Intracutaneous injection of 1 cc. of culture in each of 2 rabbits produced abscesses which broke open within thirteen days and five days, respectively, and discharged thick pus. They healed within a few days.

Intravenous Inoculations: Intravenous injection of 2 cc. of cooked meat cultures of the streptococcus, containing small particles of meat, was made into the ear veins of 4 rabbits. The particles of meat were used purposely to serve as infected emboli. Two rabbits died within a few hours; no lesions were found at autopsy. In 1 rabbit, which died within three days, there was an infarct in the lung with fibrinous pleurisy, and in the fourth, which lived for nine days, there was a large abscess in each lower lobe and a walled-off empyema between each lower lobe and the diaphragm. Pathologic sections of the lungs showed abscesses with necrosis and colonies of bacteria which appeared to be only cocci. One mouse survived an intraperitoneal injection of 0.5 cc. of culture of the streptococcus.

Comment.—This case was one of extraordinary clinical interest. On admission the patient presented physical signs suggestive of fluid in the right pleural cavity. Thoracentesis subsequently revealed a putrid empyema. The mode of production of the empyema was not clearly understood. It was thought likely that an infection of the upper respiratory tract was followed by bronchopneumonia, with the formation of an abscess which ruptured into the pleural sac. One of the most unusual features of the case was, that, although myriads of bacteria (both gram-positive cocci and gram-negative bacilli) were found in smears of the original fluid, no growth was obtained in the usual aerobic cultures, but there was an abundant growth of a short-chained streptococcus in the anaerobic cultures. A comparison of the cultural characteristics of this streptococcus with others reported in the literature will be referred to later. This organism did not remain a strict anaerobe, for after repeated transplants it grew aerobically. This coccus was responsible for the production of multiple subcutaneous abscesses, pulmonary abscesses, osteomyelitis and endocarditis. The gram-negative bacillus, which was found only in the original stained smear of the empyemic fluid, failed to grow aerobically or anaerobically.

The presence of air in the multiple subcutaneous abscesses which developed during the patient's illness was a constant finding of special interest, since the streptococcus isolated from the lesions produced gas in anaerobic meat-broth cultures.

Empyema was produced in 6 rabbits by intrapleural inoculation of an anaerobic culture of this organism. The empyemic fluid was thick and white, as is characteristic of pus found in infections of rabbits. The empyema was of long duration in 2 rabbits; one of these animals was killed within six weeks when apparently in good condition, and the other within two and one-half months. The other 4 rabbits died within from five to sixteen days. By intravenous inoculation of rabbits with culture plus meat particles as emboli it was possible to produce pulmonary lesions in 2 of 4 rabbits.

Thus an anaerobic streptococcus has been shown to be the chief etiologic agent in this patient's illness, which was fatal. Although there were many other organisms in the pleural fluid, only one produced metastatic lesions, and this was recovered repeatedly from the blood stream.

CASE 2.—*History.*—C. B., aged 28, a white laborer, single, was admitted on Dec. 19, 1931, and died on December 31. The chief complaints were a catching pain over the chest and fever of four days' duration. The family history was noncontributory. The patient's general health had been excellent. He had always been obese, weighing 270 pounds (122.5 Kg.) for several years. He was examined a year before admission by his physician and found to be in good health. Two weeks before admission he contracted a cold with a severe cough. On December 15, four days before admission, he complained of a catching pain in the left side of the chest at the level of the eighth rib; the pain gradually grew worse. He went to bed because of shortness of breath and pain in the chest. The symptoms remained the same during the next two days. The day before admission the patient became much worse. The pain shifted to the upper left region of the chest and became more severe; the appetite failed, and there were fever and increasing dyspnea. The patient coughed little, and there was never any blood in the sputum.

Physical Examination.—The temperature was 103.6 F., and the pulse rate, 130. The respiratory rate was 30, and the blood pressure, 154 systolic and 110 diastolic. The patient was a well developed, obese white man, sitting propped up in bed groaning with pain in the left side. He was oriented but seemed acutely ill. There was cyanosis of the lips and nail beds. There was no jaundice or petechiae. The tongue was coated, and the tonsils were large and edematous. A slight mucopurulent exudate was present in the pharynx. The chest showed restricted movement of the left side and signs of solidification of the left lower lobe. The heart was difficult to outline because of the obesity, but it did not appear to be enlarged. The sounds were of good quality, and no murmurs were heard. The pulse was rapid, equal and regular. There was no thickening of the radial vessels. Abdominal examination revealed nothing abnormal. The extremities were normal. There were also physical signs suggestive of Fröhlich's syndrome, i. e., female crines, small genitalia, scant hair over the face and obesity.

The red blood cells numbered 5,200,000, and the white cells, 10,840. The hemoglobin was 100 per cent (Sahli). The differential count showed 85 per cent polymorphonuclears, 1 per cent polymorphonuclear basophil leukocytes, 6 per cent lymphocytes and 8 per cent myelocytes. The red cells were normal.

Urinalysis showed: a dark amber color; specific gravity, 1.035; an acid reaction; sugar, 4 plus; albumin, 1 plus. Microscopic examination of the sediment showed a moderate number of white blood cells; there were no red cells, but there were occasional granular casts. Acetone and diacetic acid tests gave negative results.

A blood culture made under the usual aerobic conditions gave negative results. The Wassermannn reaction of the blood was negative. A culture of the throat showed Staphylococcus aureus, Streptococcus viridans, Micrococcus catarrhalis and pneumococcus, group IV.

The diagnosis on admission was: lobar pneumonia of the left lung, diabetes mellitus, hypertension and Fröhlich's syndrome.

Course in the Hospital.—An estimation of the blood sugar made immediately after the discovery of glycosuria showed 210 mg. per hundred cubic centimeters of blood. Consequently vigorous efforts were made to control the diabetes through dietary regulation and insulin. Physical examination showed extension of the pneumonic process in the left lung. The patient's temperature remained high. The white blood cells numbered 17,300. On the third day after admission the temperature remained elevated, and the patient had more pain in his chest. A roentgenogram which showed a dense shadow occupying the entire left side of the chest suggested pneumonia and a large collection of fluid. The physical examination did not, however, suggest fluid. Cyanosis and dyspnea were more marked, and the patient was put in an oxygen tent. Sugar, acetone and diacetic acid were present in the urine despite large doses of insulin. On December 23 the patient was slightly improved. The physical signs were thought to be due to consolidation without fluid. During the next two days the fever continued to be high; the white cell count remained elevated, and all of the specimens of urine showed a 4 plus reaction of sugar. The patient's condition remained the same until December 30, when signs of fluid in the left thoracic cavity became definite, and thoracentesis was done. Thirty cubic centimeters of creamy, foul-smelling, purulent fluid was removed from the left side of the chest. Smears of the fluid showed gram-positive cocci in pairs and chains, gram-negative bacilli, fusiform bacilli, a few spirilla and many pus cells. A trocar thoracotomy was done immediately, and a rubber catheter was inserted in the chest and connected with the continuous tidal drainage apparatus (Hart). On the following day, December 31, the patient became much worse. His pulse was of poor quality. The respirations were rapid and shallow. There was marked cellulitis around the site of the thoracotomy incision, and this extended over a wide area of the anterior and posterior thoracic wall. The patient grew rapidly weaker and died that evening. A blood culture taken on the day of death remained sterile when incubated aerobically. Permission to perform an autopsy was refused.

Laboratory Studies.—There was no growth from the pleural fluid aerobically on blood agar plate, or in beef infusion broth, in spite of the fact that many organisms were found on smear. Anaerobically in broth there was a granular growth at the bottom of the tube, and anaerobically on blood agar there were small colonies without the production of hemolysis. Smears of these colonies showed large gram-positive cocci, usually in pairs. The coccus was not bile-soluble. In cooked meat medium under petrolatum there was a rapid, diffuse growth with little or no gas and an extremely foul odor. Smears of the culture on meat medium showed mostly short-chained streptococci but also a moderate number of short gram-negative bacilli. This culture was transplanted to blood agar, and after two days in the anaerobe jar, two types of colony were found. One of these was found to be a pleomorphic gram-negative bacillus, possibly the influenza bacillus, and the other a gram-positive coccus. A pure culture of the coccus was obtained in meat medium, and this produced a granular growth with gas and little odor. The bacillus was not isolated in cooked meat mediums. It was thought that the anaerobic gram-negative bacillus, alone or in symbiosis with the streptococcus, was responsible for the foul odor of the cultures. The first culture of the streptococcus grew only anaerobically, but after being transplanted several times in cooked meat mediums it was found to grow aerobically also, though slowly.

Experiments in Animals.—Intrapleural injections of 1 cc. of cooked meat cultures of these organisms (predominantly anaerobic streptococci, but also a few anaerobic gram-negative bacilli) into a rabbit resulted in multiple pulmonary

abscesses on the side of the injection. There were pleural adhesions and an abscess of the anterior mediastinum. Anaerobic streptococci and gram-negative bacilli were recovered from the pulmonary abscesses and the mediastinal abscess. An injection of 4 cc. into the right pleural cavity of another rabbit resulted in death of the animal within seventeen days with massive empyema. The fluid from the chest was semiwatery, grayish white and foul, and the empyema cavity was surrounded by a thick layer of fibrin. The lung on the side of the inoculation was a reddish, compressed, necrotic mass. A smear of the pus showed an abundance of streptococci and a moderate number of gram-negative bacilli. The streptococcus recovered from this empyema grew aerobically within three days and showed good growth anaerobically within twenty-four hours. It did not produce hemolysis. Intravenous injections of this organism into two rabbits, cultures on cooked meat mediums being used, with particles of meat for emboli, resulted in no pulmonary lesions. Intracutaneous injection failed to produce a lesion.

Comment.—The patient was acutely ill on admission, and the signs of intoxication were marked. The pulmonary infection was complicated by a severe diabetes, which was difficult to control. A putrid empyema later developed for which thoracotomy was done with drainage of the large amount of fluid, but this failed to avert the fatal outcome, and the patient died with evidences of profound toxemia. A variety of organisms were found on smears of the empyemic fluid. Anaerobic culture yielded a streptococcus and gram-negative bacillus. The streptococcus was a facultative anaerobe. It was usually found with an anaerobic gram-negative bacillus (unidentified) but could be isolated in pure culture. It produced a small amount of gas with only a slight odor (when free of the bacillus) in cooked meat medium. It failed to produce hemolysis on blood agar. Cultures of the streptococcus produced a massive empyema in 1 of 4 rabbits on intrapleural inoculation and abscesses of the lung and mediastinum in another rabbit. Intravenous and intracutaneous inoculations gave negative results.

Case 3.—*History.*—A. P., aged 52, a colored cook, married, was admitted on Dec. 5, 1932 and died on December 22. The chief complaints were pain in the left side and cough for three days. The family history was noncontributory. The patient's general health had been fairly good. He had an attack of jaundice at 7 years of age, malaria at 9 years, typhoid fever at 15 and right-sided pleurisy many years before admission. At 30 he had an illness described as rheumatism, which lasted for one and one-half weeks and involved the joints of the left leg, right arm and hand. He had been a heavy drinker for many years. For two weeks prior to admission he had felt unwell because of a cold and cough. On December 2, three days before admission, he had a shaking chill and a sharp pain in the lower part of the left axilla, accentuated by breathing. There were marked malaise and nausea, but no vomiting. The following day the thoracic pain persisted; the chills recurred, and the pain shifted to the upper part of the axilla. The patient vomited once on this day. On the day before admission, December 4, the cough became worse and was productive of a white phlegm. The sputum was never rusty or blood-streaked. On the day of admission, all of the symptoms became aggravated, and the patient was admitted to the medical ward.

Physical Examination.—The temperature was 103 F. The pulse rate was 80 and the respiratory rate, 52. The blood pressure was 160 systolic and 110 diastolic. The patient was a husky colored man lying on the right side in acute respiratory distress. He was obviously ill but alert and oriented. Respirations were rapid, shallow and grunting, and there was dilatation of the alae nasi at every breath. He coughed up a small amount of foamy white sputum. There was no jaundice or cyanosis. The pupils reacted normally but were irregular. The mouth was foul because of dental caries. The pharynx was injected. The trachea was in the midline. The chest was well formed. There was great limitation of motion in the left region of the chest, particularly in the lower portion. The right side moved normally and was normal to percussion and auscultation. A leathery friction rub was heard in the left anterior axillary line. Anteriorly, the left region of the chest was normal; posteriorly, for three fingerbreadths above the normal base there was dulness to percussion; the breath sounds were high-pitched, and expiration was prolonged. The breath sounds were not definitely tubular. The heart was not enlarged. The point of maximum impulse was 8.5 cm. to the left in the fifth space. The heart sounds were regular and slow. At the base the aortic and pulmonic second sounds were accentuated equally. The aortic second sound was ringing and preceded by a blowing systolic murmur. The abdomen was soft and not distended.

The red blood cells numbered 4,810,000, and the white cells, 12,760. The hemoglobin was 68 per cent (Sahli). The differential count showed juvenile polymorphonuclears, 6 per cent; adult polymorphonuclears, 65 per cent; monocytes, 7 per cent, and lymphocytes, 22 per cent. The red cells showed slight achromia. Urinalysis showed: amber-colored and clear urine; specific gravity, 1.018; reaction, acid; sugar, negative; albumin, negative; in the sediment, no red blood cells, white blood cells in moderate number, with occasional clumping, and an occasional granular cast; acetone, negative; *di*-acetic acid, negative; bile, negative; urobilin, 4 plus.

The diagnosis on admission was: lobar pneumonia of the left lower lobe on the fourth day of illness; chronic alcoholism, delirium tremens, arteriosclerosis and hypertension.

Course in the Hospital.—For the first week of the patient's illness in the hospital, the temperature was constantly elevated, varying between 101 and 104 F., with corresponding tachycardia and a rapid respiratory rate. The white blood count during the first two or three days varied between 11,000 and 22,000. Three days after admission a pleuropericardial friction rub was heard over the left lower region of the chest. Cultures from the sputum showed green streptococci, Staph. aureus and diphtheroids. No pneumococci were found. Roentgenograms of the chest showed consolidation of the left lung. On December 9 there was spread of the pneumonic process to the base of the right lung. On December 11 the patient was still acutely ill, with signs of solidification of the left lower lobe but fewer signs at the right base. He was semidelirious. On December 12 he lost about 200 cc. of blood by rectum because of bleeding hemorrhoids. On December 13 he was disoriented and irrational. On December 15 the development of suppression of breath sounds and voice sounds and a flat percussion note at the right base indicated the presence of fluid. Thoracentesis was performed, but no fluid was obtained. On December 16 the temperature still varied between 100 and 102 F., and the physical signs in the lungs showed few changes. A friction rub heard at the apex of the heart was thought to be a pericardial rub. On December 17 it was noted that the patient's sputum, which previously had been mucopurulent and

occasionally blood-tinged, had become more purulent and extremely foul in odor. Physical signs showed a rapid respiratory rate, tympany at the left base posteriorly and an area at the angle of the left scapula where the breath sounds were faintly tubular. There were many râles of a metallic quality in this region. Pleural friction rub still persisted. Smears of the sputum showed numerous spirochetes and fusiform bacilli. In view of the atypical pneumonia it was thought that the patient probably had a pulmonary abscess. On December 18 he was given a transfusion of 500 cc. of citrated blood without a reaction. On December 19, in view of persistent signs at the angle of the left scapula, a second thoracentesis was done, but no fluid was obtained. On December 20 the friction rub over the left side of the chest was still present, and the heart was found to be displaced to the right. Blood cultures taken on admission and on three subsequent occasions gave negative results. Roentgenograms of the chest showed "areas of consolidation involving the entire left lung with an area of lesser density suggesting lung abscess; bronchopneumonia right lung." On December 22 the patient complained of attacks during which he could not get his breath. He was exhausted and obviously weaker; the respiratory rate was as high as 80 per minute. The patient was coughing up a small amount of foul sputum. There was no deviation of the trachea. There were indefinite signs of solidification in the right middle lobe and signs of shifting dulness in the left side of the chest indicative of hydropneumothorax. A third thoracentesis was done in the left side of the chest, posteriorly. Three hundred cubic centimeters of creamy, brownish, fetid, purulent fluid was removed. During the process of removal a little air was obtained in the syringe, and when the patient coughed the plunger was forced outward with the air. More fluid could have been obtained, but the patient was so weak that the procedure was stopped. He died shortly after the thoracentesis.

Autopsy.—The anatomic diagnosis was: lobar pneumonia of both lungs and multiple abscesses of the left lower lobe, with organization of the surrounding exudate; a bronchial fistula and empyema on the left side and fibrinous pleurisy of the right side; an acute splenic tumor; hyperplasia of the bone marrow; multiple gummas and scarring of the liver; slight arteriosclerosis, and scars in the pancreas.

Laboratory Studies.—The pleural fluid was grayish brown, moderately thick and foul in odor. A smear showed a predominance of gram-negative bacilli and gram-positive cocci. There were also a few fusiform bacilli. There was no growth aerobically, but when the exudate was inoculated into cooked meat medium under petrolatum there was a diffuse growth with gas and a foul odor. A smear of this showed gram-positive cocci (very small and often in short chains) and thin, rather long gram-negative bacilli. Anaerobic culture of this cooked meat culture on blood agar produced small colonies of viridans streptococci; the gram-negative bacilli did not grow on blood agar, aerobically or anaerobically. The anaerobic meat-medium culture was also transferred to blood agar and left under aerobic conditions. There was a slow growth in three days of fine colonies showing viridans hemolysis, which proved to be gram-positive cocci. The colonies of cocci from the anaerobic blood agar plate were then put into plain broth (not anaerobic) and in meat medium under petrolatum. In both there resulted a good growth without the production of gas or odor. The organism was not soluble in bile and produced acid in dextrose, maltose and sucrose but not in lactose or mannite.

A rabbit was given an intrapleural injection of 3 cc. of the meat medium culture. The animal was killed two months later, but no lesion was found except a few pleural adhesions on the side of the injection.

Comment.—On admission the patient was thought to have lobar pneumonia of the left lower lobe in the fourth day of the disease. The physical signs were not classically those of lobar solidification, however, and numerous cultures of the sputums with inoculations into mice failed to reveal pneumococci. As the disease progressed during the first week, pleural and pleuropericardial friction rubs were conspicuous. During the second week the sputum, which had formerly not been offensive, became foul. Physical signs over the left lower lobe plus the foul sputum suggested a pulmonary abscess, and this was confirmed by roentgenograms. During the third week the patient remained critically ill, and signs of a left hydropneumothorax developed. This proved to be a pyopneumothorax, as 300 cc. of foul-smelling fluid plus air was removed from the left side of the chest. The suspicion at the time of death of confluent bronchopneumonia with pulmonary suppuration, a bronchopleural fistula and putrid empyema was confirmed at autopsy. The autopsy showed numerous abscesses, one of which was in open communication with the pleura, and it was evident that the rupture of this abscess into the pleural cavity was responsible for the putrid empyema.

The empyemic fluid contained a number of organisms. Gram-negative bacilli and gram-positive cocci were in equal number, and there were similar numbers of fusiform bacilli. The smears of sputum showed numerous fusiform bacilli and spirilla. Cultures of the pleural fluid yielded a facultative anaerobic green streptococcus and an unidentified small gram-negative bacillus (possibly the influenza bacillus). The streptococcus was the only organism which could be carried on through subsequent cultures. Although at first it grew only anaerobically, subcultures later grew fairly well aerobically. This streptococcus alone or in symbiosis with other anaerobic organisms seems to have been responsible for the patient's pneumonia and empyema.

CASE 4.—*History.*—S. C., aged 53, a colored carpenter, was admitted on April 27, 1932. He was discharged on July 12. The chief complaints were shortness of breath and pain in the right side. The family history was not obtained. The patient was too ill to give an account of his previous condition. His general health, however, had been excellent. He was in good health until seven weeks before admission when he contracted a cold and had a sharp pain in the chest, accompanied by chill, malaise, fever and a cough with yellowish sputum. The illness was diagnosed as pneumonia by his physican. Within two weeks he was somewhat improved. Four weeks before admission a dull, aching pain developed in the right lower region of the chest and in the upper part of the abdomen. The cough persisted and was productive of mucoid but not purulent sputum. The appetite failed; pain persisted intermittently; he had frequent sweats at night and chills, and for a considerable period was delirious.

Physical Examination.—The temperature was 102.4; the pulse rate, 102; the respiratory rate, 36; the blood pressure, 150 systolic and 98 diastolic. The patient looked acutely ill and complained of severe pain in the right side of the chest and the upper part of the abdomen. There were dyspnea, orthopnea and cyanosis.

An infrequent cough was productive of tenacious sputum. The teeth were in poor condition. The pharynx was injected. The heart was not enlarged; the rate was rapid but regular, and no murmurs were heard. The chest showed elevation of the left side of the diaphragm and normal pulmonary resonance on this side; on the right there was dulness below the fourth rib anteriorly and the seventh spine posteriorly, with distant to absent breath sounds and occasional coarse râles. The abdomen showed fulness in the right upper quadrant and an enlarged, tender liver. The spleen and kidneys were not felt. Large internal hemorrhoids and a firm prostate were found on rectal examination.

On admission the blood showed 3,520,000 red cells and 16,500 white cells. The hemoglobin was 55 per cent (8 Gm.). The differential count showed: polymorphonuclears, 61.7 per cent; myelocytes, 17.2 per cent; lymphocytes, 20.3 per cent and monocytes, 0.8 per cent. The blood smear showed that the red cells were smaller than normal, with central pallor. There was a shift to the left in the granulocytes. Urinalysis on admission showed: yellow, clear urine; specific gravity, 1.013; reaction acid; sugar, negative; albumin 1 plus. Microscopic examination of the sediment showed a moderate number of white blood cells, but no red cells, and a moderate number of granular casts.

The diagnosis on admission was empyema at the right base, with possible subdiaphragmatic abscess on that side.

Course in the Hospital.—A roentgenogram of the chest confirmed the impression of fluid at the right base. Thoracentesis was done immediately, and with the needle in the eighth interspace in the posterior axillary line 8 cc. of thick, greenish-yellow, foul-smelling pus was removed. During that afternoon the patient had a shaking chill with a rise in temperature to 105 F. Trocar thoracotomy was performed, and a rubber catheter was inserted and connected with the continuous tidal irrigation apparatus (Hart). On April 28 there was considerable drainage of pus from the catheter. The patient was given a transfusion of 500 cc. of citrated blood with no reaction. The number of white blood cells increased to 14,400. The temperature remained between 101 and 104 F. On April 29 the temperature was lower, but the patient was still critically ill. Physical signs in the chest had changed little. The respirations were rapid and shallow. The catheter was draining freely. The abdomen was markedly distended, and the tenderness in the right upper quadrant persisted. There was still thought to be a possibility of a subdiaphragmatic abscess, but no further operative procedures were done. During the next three or four days there was a gradual decline in the fever. The pulse remained accelerated. The white blood cell count remained between 16,000 and 20,000. The patient was delirious at times. Blood cultures taken on admission aerobically and anaerobically showed no growth. Culture of the sputum showed green streptococci and hemolytic and nonhemolytic staphylococci. The smears showed no acid-fast bacilli. On May 6 there were definite signs of improvement. The patient looked much better, but the temperature still remained elevated, and signs of solidification of the right lower lobe persisted. Abdominal distention was less, and the tenderness was somewhat reduced. On May 9 and 10 the temperature chart showed an evening peak of 103 F., with corresponding tachycardia. The cough was less, and the sputum not offensive or bloody. There were many moist râles at the left base posteriorly. The right side of the chest was clear anteriorly, but dulness and distant tubular breathing were still present posteriorly at the base. The rises in temperature suggested an area of pus which was not being adequately drained.

During the next week his condition changed only a little. On May 19, because of the patient's continued improvement and the diminution in drainage from

the chest, the use of the irrigation apparatus was discontinued, and the catheter left in place. Thoracentesis of the right side of the chest was again performed, but no fluid was obtained. Following the removal of the apparatus for drainage, the temperature fell to normal and remained there for three days. An abscess in the subcutaneous tissues surrounding the catheter was opened, and a large amount of pus evacuated, from which was grown Bacillus pyocyaneus and diphtheroids.

The patient continued to improve, and on May 31 the catheter in the chest was removed. The patient coughed up daily about 200 cc. of frothy sputum. Smears were repeatedly negative for acid-fast bacilli. The signs in the lungs slowly cleared.

During the month of June convalescence continued. The temperature remained normal but tachycardia persisted. The electrocardiographic studies showed no abnormalities. On July 1 the patient was up and around the ward, feeling much improved. The cough and the pulmonary signs gradually cleared. The blood responded slowly to therapy with an iron preparation. The patient was discharged on July 12. Roentgenograms taken shortly before discharge showed only the evidence of a thickened pleura.

Laboratory Studies.—The pus obtained from the pleural cavity was rather thick, greenish-white and foul. No spirochetes were found on smear or on dark field examination. Smears showed many gram-positive cocci in short chains. In addition, there were many groups of large curved, weakly gram-negative bacilli. They were always found in small groups, consisting of about ten organisms intertwined in a characteristic manner. These gram-negative bacilli did not grow in subcultures, and they were never identified satisfactorily, as they did not correspond to any organisms that we had observed in pleural fluids up to that time. Some observers thought they were fusiform bacilli, though they were weakly gram-negative. In some ways they resembled an organism described by Harris and Brown [29] and isolated from the uterus in 6 cases of puerperal infection. This was a pleomorphic gram-negative bacillus, often long and curved or beaded, and sometimes branching. They called it Actinomyces pseudonecrophorus, as it was much like Actinomyces necrophorus—an organism which is very pathogenic for animals and which produces lesions of a gangrenous and ulcerative character in many different species of animals. It is a strict anaerobe and is killed by a brief exposure to air. The possibility that this was the organism with which we were dealing became more plausible when we learned that Shaw has recently [30] reported the isolation of A. necrophorus from a pulmonary abscess in a man, and that it has been found responsible for various lesions in man, such as a pseudodiphtheria, abscesses of the tissues of the hip joint and retropharyngeal abscesses with gangrene.

Aerobic broth culture showed a slight growth of streptococci at the bottom of the tube, but there was no growth when this was transferred to blood agar. Anaerobically in cooked meat medium there was a diffuse growth of gram-positive cocci, with no gas and a moderately foul odor. Aerobic culture of the original pus on blood agar gave no growth, but subsequent culture on blood agar from the meat medium resulted in a slow growth of the streptococcus, with the production

29. Harris, J. W., and Brown, J. H.: Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, Bull. Johns Hopkins Hosp. **40**:203 (April) 1927.

30. Shaw, F. W.: Science **77**:392 (April 22) 1932.

of a small amount of hemolysis. Anaerobic culture on blood agar gave a good growth of pure culture of a green streptococcus.

The original pus injected into the pleural cavity of a rabbit produced large, walled-off empyema with thick white, odorless pus, a smear of which showed gram-positive cocci. Injection of this streptococcic culture (5 cc. intrapleurally) into another rabbit gave negative results. Intravenous injection also gave negative results.

Comment.—In this case the anaerobic streptococci were found in the pleural fluid in association with an unusual type of gram-negative bacillus which was never satisfactorily identified. No spirilla were seen on smears of this fluid, and none was demonstrated in the sputums. The improvement of the patient was slow but definite under continuous irrigation of the pleural cavity with saline solution. He was discharged from the hospital after two and one-half months, greatly improved.

Brief mention may be made of three cases other than those of putrid empyema in which anaerobic streptococci were recovered. In 2 of them the organism was isolated from pus obtained from pulmonary abscesses at the time of operation; in the remaining case the organism was obtained from hepatic abscesses post mortem.

Case A.—The patient, H., had an acute pulmonary abscess. At operation foul, moderately thick pus was obtained. Smears of the pus showed many spirochetes, fusiform bacilli and gram-positive cocci. The cocci proved to be streptococci which grew slowly aerobically on blood agar. In beef infusion broth there was slight granular growth at the bottom of the tube. Anaerobically, in cooked meat medium and on blood agar, there was rapid growth with a slight amount of hemolysis. The cooked meat medium produced a diffuse growth with gas and a foul odor. The organism was found to ferment sucrose, dextrose, lactose and maltose, but not mannite. Two rabbits received intrapleural injections of culture of twenty-one to twenty-four hour cooked meat medium of this streptococcus. One was killed after one month, and the other after one and one-half months, though both animals appeared in good condition. In 1 an abscess was found in the pleuropericardial region, with adhesions to the right lung and heart. There was no growth from the pus, which was cultured aerobically, but anaerobically in meat medium there was a pure culture of streptococcus. Anaerobically on blood agar there was a growth of small colonies after four days. Smears of the colonies showed a short-chained streptococcus and a gram-negative bacillus which did not grow on subsequent subculture. In the other rabbit the only lesions found were pleural adhesions on the side of the injection. Intracutaneous inoculation of 0.5 cc. of the culture of streptococcus resulted in a firm abscess with no redness of the skin.

This was therefore an organism which was found associated in the original pus with spirochetes and fusiform bacilli. In pure culture it was a streptococcus growing well anaerobically, with production of gas and a foul odor; aerobically it grew poorly. It was of low virulence for rabbits on intrapleural injection.

Case B.—The patient, S., had a chronic pulmonary abscess. Thick, brown, foul pus was obtained at operation. Smears showed spirochetes, fusiform bacilli and gram-positive cocci. Cultures resulted in the growth of a green streptococcus

growing better anaerobically than aerobically (it grew aerobically only after repeated transplants), with no gas but with a foul odor on meat medium.

CASE C.—G, a white man, aged 25, was admitted because of fever, epigastric pain, chills, nausea and vomiting of seven days' duration. On admission he was acutely ill, with a temperature of 106 F. and tachycardia of 124. Physical examination revealed little except tenderness in the epigastrium and leukocytosis of 50,000. The diagnosis on admission was obscure. The possibilities suggested were pneumonia, an infection in the kidney or an infection in or about the liver. The epigastric pain continued with nausea, vomiting, irregular fever and leukocytosis. The patient later became jaundiced. He died in uremia, with complete suppression of urine. Autopsy showed multiple hepatic abscesses, subacute appendicitis and thrombosis of the portal vein, with infection of the portal branches within the liver. Although three blood cultures were taken during life and incubated aerobically, none showed any growth. Cultures of the heart's blood and the hepatic abscesses at autopsy revealed two organisms: (1) an anaerobic beta hemolytic streptococcus fermenting lactose, dextrose, sucrose, salicin and maltose but not mannite, inulin or raffinose; this organism conformed to the Streptococcus intermedius of Prévot, and (2) an unidentified short, slender anaerobic gram-negative rod.

This case was puzzling clinically and was settled only by postmortem examination. The infection most likely began with an attack of appendicitis with subsequent pylephlebitis and hepatic abscesses. The importance of incubating the blood culture anaerobically should be mentioned in this connection.

COMMENT

This report deals with the clinical and bacteriologic observations in 7 cases of putrid purulent infections from which anaerobic streptococci were isolated. Six of the patients suffered from acute respiratory infections, and 1 from hepatic abscesses. Anaerobic streptococci were the only organisms recovered culturally in 6 of the cases, and in the other they were abundantly present with a mixed flora. The significance in pathogenesis, which the predominance of this type of bacteria suggested, was supported by experimental results in rabbits.

The 4 patients who had putrid empyema were men; 3 of them died. In the cases with a fatal outcome the duration of the disease was from sixteen days to two months. The patient, who recovered, had a prolonged illness which lasted four months.

From the clinical standpoint the cases are of interest in that the putrid empyema developed acutely and suddenly and was not a complication of a preceding chronic pulmonary infection. The studies indicated, however, that the pleural infection was associated with intrapulmonary infection. This relationship was proved in 2 of the cases which were examined post mortem.

The fluid aspirated from the pleural cavity had a characteristically offensive odor and was moderately thick, varying in color from brownish-gray to green. A stained smear of this pus at the time of the first aspiration in each case revealed myriads of bacteria of various

types. Spirochetes and fusiform bacilli were found in 2 cases, and a gram-negative bacillus (usually short but at times long and thin) was present in 3. There was a gram-positive coccus (usually predominating) in all 4 cases. In 1 there were in addition to the coccus, many small groups of long, curved gram-negative bacilli; these were always found in isolated groups and were intertwined in a characteristic manner.

Bacteriologically, the cases were complex. It seems to us of interest, however, and probably significant, that anaerobic streptococci were present in each case, although the associated organism, which constituted the flora, was not consistently of one type. Furthermore, that the method of laboratory cultivation is of special importance is demonstrated by the fact that streptococci were chiefly recovered under anaerobic conditions, when the usual aerobic methods failed. The results are illustrative of the importance of considering cultural and environmental factors when one attempts to isolate bacteria from pathologic lesions. Of the four strains of streptococci, two were viridans, one nonhemolytic and one hemolytic. They grew in short chains and produced a granular growth in cooked meat mediums beneath a petrolatum seal, usually with a foul odor. Though they could be grown only slowly or not at all under aerobic conditions, subsequent transplants from the original fluid showed a definite though slow growth aerobically. There was always a luxuriant growth anaerobically. In biologic and cultural characteristics they resemble in some ways the Streptococcus putridus of Schottmüller and the Streptococcus intermedius of Prévot. The latter organism was found in pulmonary conditions, but both these types are described as strict anaerobes, whereas ours were facultative anaerobes. Another of Prévot's group is referred to as "anaerobes by predilection," the first cultures growing only anaerobically, while subcultures grow aerobically also. This group Prévot called "Streptococcus evolutus," and most of the strains were isolated from pulmonary conditions. If an attempt is made to classify the streptococci which we are reporting under any one heading, they would seem to correspond to the latter group more closely than to any other.

We have reviewed the subject of putrid empyema because it is not an extremely uncommon sequel to pulmonary suppuration of various types; when it develops, the prognosis becomes grave. We have also made special reference to an anaerobic streptococcus which was found in the 4 cases reported because it is an organism that is found throughout the body in various putrid and gangrenous lesions. Its presence is apt to be overlooked unless anaerobic cultures are taken. Our studies indicate that it was the chief etiologic agent in the 4 cases of putrid empyema, in 1 of which it invaded the blood stream, produced multiple metastatic abscesses and endocarditis and was obviously the cause of death.

Although the therapeutic side has not been emphasized in this report, surgical drainage would seem to offer the best chance of cure. Intravenous injections of neoarsphenamine are probably of value in cases in which spirochetes are found, especially if they are also in the sputum. Extensive cellulitis of the thoracic wall, with the formation of gas, may follow surgical drainage or aspiration, owing to the leakage of the organisms along the path of the needle or the incision. A therapeutic procedure that may offer additional help in dealing with such effusions, swarming as they are with anaerobes, is the replacement of the empyema by air. We have had no experience with this form of treatment of empyema, but favorable results have been reported by Danna and others in all forms of empyema.

SUMMARY

1. Attention is called to the fact that infections due to anaerobic streptococci may occur frequently and fail to be recognized unless cultivation is properly performed.

2. A case is reported of putrid empyema with pulmonary abscesses, septicemia and metastatic putrid abscesses due to a gas-producing, facultative anaerobic streptococcus.

3. Other cases of putrid empyema are reported in which an anaerobic streptococcus was found in conjunction with other organisms.

4. Anaerobic streptococci were found to be the predominant organisms in 2 cases of pulmonary abscess in which cultures were made directly from the pus at operation. Other authors have stressed the frequent occurrence of these organisms in such lesions.

5. Although the finding of anaerobic streptococci in cases of pleural and pulmonary disease has been emphasized, the literature indicates their frequent occurrence in other infections, notably in cases of puerperal sepsis or septic abortion, otitis media, pulmonary abscesses and hepatic abscesses.

6. Mention is also made of a case of pylephlebitis with multiple hepatic abscesses due to an anaerobic streptococcus. An attempt is made to identify the streptococci reported with various types described in the literature. They do not completely fulfil the characteristics of any one group.

7. Cultures of one strain were capable of producing empyema in rabbits when injected intrapleurally. Other strains gave varying results under similar conditions.

8. Evidence is presented to indicate that these streptococci may often be pathogenic for man and for animals.

UNILATERAL AND BILATERAL RESECTION OF THE MAJOR AND MINOR SPLANCHNIC NERVES

ITS EFFECTS IN CASES OF ESSENTIAL HYPERTENSION

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On the basis of postmortem investigation and theoretical consideration, section of the splanchnic nerves was suggested by Jean [1] in 1921 for the relief of pyloric spasm, hyperacidity and hypersecretion. In 1923 Daniélopolu,[2] considering the importance of the splanchnic nerves in the regulation of arterial pressure, conceived the idea of their resection in the treatment of hypertension. In the same year, Brüning [3] suggested the same surgical procedure, and in 1924 Pende [4] proposed before the Congress of Internal Medicine at Milan surgical treatment of arterial hypertension which consisted of resecting the left splanchnic nerves. In 1927 Pieri [5] performed unilateral resection of the splanchnic nerves for intestinal atony. In 1930 Pieri,[4] following the suggestion of Pende, successfully resected the left splanchnic nerves of two patients suffering from arterial hypertension. In 1932, Durante,[4] of Genoa, resected the large and small left splanchnic nerves of two patients suffering from different arterial diseases. These cases were reported by Santucci,[6] and although they were not true cases of hypertension, the postoperative observation indicated a fall in both systolic and diastolic pressures. In giving a résumé of the surgical technics which have been described in the literature, Pereira [7] stated that

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1. Jean, G.: Les nerfs splanchniques au point de vue chirurgical, Arch. de méd. et pharm. nav. **111**:292, 1921.

2. Daniélopolu, quoted by Pereira.[7]

3. Brüning, Friedrich, and Stahl, O.: Die Chirurgie des vegetativen Nervensystems, Berlin, Julius Springer, 1924.

4. Quoted by Santucci.[6]

5. Pieri, Gino: La resezione dei nervi splancnici, Ann. ital. di chir. **6**:678 (July) 1927.

6. Santucci, Gastone: La thérapeutique chirurgicale de l'hypertension artérielle selon la méthode de Pende, Clinique, Paris **27**:9 (Jan.) 1932.

7. Pereira, António: Nervi splaenchnici, Porto, Portugal, Tipografia Porto Medico, Ltd., 1929.

Pieri's technic consisted of resection of the splanchnic nerves by means of the supradiaphragmatic approach after resecting the tenth, eleventh and twelfth ribs. Rossi [8] attacked the splanchnic nerves between the attachments of the diaphragm after resecting the transverse process of the eleventh and twelfth thoracic vertebrae and the twelfth rib when necessary. Pereira objected to the two previous technics because of the danger of injuring the pleural sac and proposed section of the splanchnic nerves below the diaphragm without resection of bony structures.

In 1925 Rowntree and Adson [9] performed bilateral lumbar sympathetic ganglionectomy on a patient with hypertension. The beneficial effects were only transient, and later Adson attempted to relieve hypertension associated with severe headaches by removing the cervicothoracic sympathetic ganglions. In both cases it was the opinion that insufficient vascular areas had been affected by the operation. In 1930 Adson and one of us (Craig) divided the right and left anterior roots of spinal nerves from the sixth thoracic to the second lumbar ganglions; the patient was a young adult who had a severe form of essential hypertension. The operation was followed by definite improvement in the hypertension, but, because of the manipulation of the spinal cord that it entailed, extensive resection of the nerves was not considered a satisfactory method of combating the changes in the blood pressure.

The splanchnic nerves are composed of preganglionic fibers which emerge from the spinal cord through the anterior roots and enter the thoracic sympathetic ganglionated trunk by means of communicating rami. These fibers traverse the ganglions and make their exit by means of fibers given off by the fifth to the twelfth thoracic ganglions. The major splanchnic nerve is usually composed of fibers from the fifth to the tenth ganglions, and the minor splanchnic nerve of fibers from the last two dorsal ganglions. The splanchnic nerves leave the thoracic cavity and enter the abdominal cavity between the crura of the diaphragm. It is at this point that resection is carried out.

PATHOGENESIS OF ESSENTIAL HYPERTENSION

Of the various hypotheses concerning the etiology of essential hypertension, the most acceptable is that the condition is of neurogenic origin. Hypersensitivity or hyperreactability of the vasomotor nervous mechanism is postulated. Whether this abnormality is of central origin, that

8. Rossi, Ferdinando: La resezione del tronco simpatico toracico e dei nervi splancnici nello spatium inframediastinale posterius, Arch. ital. di chir. **21**:729, 1928; abstr., Zentralbl. f. Chir. **56**:1334, 1929.

9. Rowntree, L. G., and Adson, A. W.: Bilateral Lumbar Sympathetic Neurectomy in the Treatment of Malignant Hypertension, J. A. M. A. **85**:959 (Sept. 26) 1925.

is, whether there is a hypersensitive vasomotor center, lowered tonus of the cardio-aortic and carotid sinus reflex zones or some abnormality of the peripheral mechanism, is not known. The experimental evidence of Raab [10] is that an increase in the concentration of carbon dioxide in the blood augments the vasopressor effects by action on the vasomotor centers. Similar increase in the reactions of hypertensive subjects is obtained by means of stimulation by cold.[11] Clinical evidence favors a central basis for the abnormality in essential hypertension for the following reasons: 1. The vasoconstrictor disturbance is widely distributed. 2. Analogies to other sympathetic disturbances of the central mechanism exist, such as disturbance of the heat-regulating centers in certain lesions of the brain. 3. Demonstrable pathologic abnormalities in the arterioles, endocrine glands or sympathetic nerves of subjects with the earliest forms of hypertension are not found. It is probable that after organic changes have occurred in the arterioles, peripheral pressor effects constitute a superimposed pressor factor. Renal sclerosis and insufficiency add a further peripheral pressor element. The part played by pressor hormones is not clear, but may be important. Although the etiology of the fundamental pathologic change is unknown, attempted control of the abnormal central vasopressor reactions is logical. A similar problem exists in Raynaud's disease, control of which is made possible by blocking the efferent pathways to the vessels. In the early stages of this disease, evidence indicates hyperreactability of the centers in the spinal cord. At this stage, resection of the sympathetic ganglions effects clinical cure. In the more advanced stages, Lewis [12] wrote, a peripheral "fault or demonstrable organic occlusion of the smaller digital arteries superimposes an additional factor, not completely controlled by section of the sympathetic nerves."

RATIONALE OF SPLANCHNIC SYMPATHECTOMY

Maintenance of the blood pressure involves two mechanisms. One mechanism maintains the systemic blood pressure at optimal levels. The factors involved in this are multiple. Maintenance of blood pressure is not materially affected by removal of the sympathetic nerves, as has been shown by Cannon.[13] The other is a mechanism of response, involv-

10. Raab, W.: Central Vasomotor Irritability; Contribution to the Problem of Essential Hypertension, Arch. Int. Med. **47**:727 (May) 1931.

11. Hines, E. A., Jr., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions: Its Application in the Study of Hypertension, Proc. Staff Meet., Mayo Clin. **7**:332 (June 8) 1932.

12. Lewis, Thomas: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, Heart **15**:7 (Aug.) 1929.

13. Cannon, W. B.: Personal communication to the authors.

ing rapid increases of the blood pressure to stimulation: psychic, sensory and otherwise. It is the "response" or vasopressor reactions which we wish to emphasize in writing of the therapeutic endeavors in hypertension.

Recent studies have shown that the hypertensive response of the blood pressure in cases in which the earliest forms of essential hypertension are present is the sole abnormality as yet demonstrated. With a standard stimulus (local application of cold) it has been shown that the blood pressure of normal subjects and of patients with diverse types of diseases momentarily increases; the increase averages 10 mm. of mercury systolic and 8 mm. diastolic. In the cases of mild or early essential hypertension the average increase is three times greater than this. In the more advanced types of hypertension, increases of from three to six times the normal response are obtained. A group of young subjects from 16 to 30 years of age, apparently normal, in the immediate families of 75 per cent of whom hypertension had appeared, have had reactions of the same magnitude as have subjects with early hypertension. These we have called the "hyperreactive normals." This suggests that the vasopressor mechanism of subjects predisposed to essential hypertension is constitutionally abnormal, the abnormality expressing itself as an excessive reaction to stimulation. The reaction is of the same order as that of normal subjects, except that it is magnified. If this is true, this functional stage of essential hypertension assumes an important part in the explanation of the evolution of the disease and of the subsequent organic changes in the arterioles. These excessive reactions constitute abnormal degrees of arteriolar "wear and tear." The problem of treatment of hypertension, then, will involve endeavors to block or modify these excessive responses before the onset of organic or irreversible lesions in the arterial tissues, with ensuing high blood pressure.

Selection of Cases (Theoretical Consideration).—In the clinical forms of essential hypertension, two groupings are possible, the functional or "preorganic" and the organic types. This distinction can be made on the basis of the appearance of retinal arterioles and by quantitative studies of the arterioles in a specimen of muscle removed for biopsy. In some cases this division is clear; in others, both organic and spastic elements are present. The existence of a spastic form of retinitis, as described by Wagener in organic types of hypertension, has helped to clarify this concept. The excessive response of blood pressure to stimulation has given further evidence of the spastic element in certain types of essential hypertension. Certain subjects with hypertension have periods in which the blood pressure is excessively labile. The problem in selection of the type of subject who is suitable for resection of the splanchnic nerves entails recognition of the degree in which the case exemplifies these two factors, the spastic or vasomotor

and the organic. The first is concerned with abnormal fluctuation of the blood pressure and the second with levels of the blood pressure attained under resting or basal conditions. To evaluate these components before operation is important, for removal of the vasomotor control of the splanchnic bed would, theoretically, modify only the vasomotor element.

Procedures.—The maximal reactions of the blood pressure are determined by application of cold and by carbon dioxide tests. The increase and the maximal level attained then become the criteria with which the effects of subsequent therapeutic measures can be compared. Hourly readings of blood pressure are taken for twenty-four hours under controlled conditions, and the mean resting levels and hourly fluctuations are determined.

In spinal anesthesia procaine hydrochloride in doses of from 60 to 75 mg. is employed. The blood pressures are taken every fifteen minutes, and the cold test is repeated at frequent intervals. With anesthesia to the level of the nipple the responses of the blood pressure to cold are greatly reduced or obliterated, and the splanchnic chemical denervation should be complete. In addition to anesthetization of the sympathetic nerves the motor and sensory fibers of the lower limbs and abdominal wall are also temporarily blocked. Vasodilatation of the surface vessels of the toes is taken as evidence that the sympathetic nerves are anesthetized. Emmett's [14] studies with spinal anesthesia revealed that sympathetic, sensory and motor nerves are anesthetized in the order named. Preoperative studies with spinal anesthesia were made to obtain information concerning the extent cephalad to which anesthesia must be induced to diminish or inhibit the pressor reactions and to determine the probable effects of splanchnic denervation on these responses. The organic changes are evaluated by measurements of the arterioles in a specimen of muscle removed for biopsy, by the appearance of the arterioles in the ocular fundi and by the basal blood pressures. The age of the patient and the function of the heart or kidneys and other clinical criteria are of major importance in deciding on operability.

RESECTION OF SPLANCHNIC NERVES AND POSTOPERATIVE COURSE

The technic which we have adopted consists of the posterior, infradiaphragmatic approach, with the incision in the skin extending from the level of the eleventh rib to the crest of the ilium, about 6 cm. from, and paralleling, the spines of the vertebrae. The posterior layer of the lumbodorsal fascia is incised almost to the level of the twelfth rib above and to the crest of the ilium below, and the fibers of the serratus posterior inferior muscle are divided, exposing the sheath of the sacrospinalis muscle. This sheath is then divided about 2 cm. mesial to the lateral

14. Emmett, J. L.: Subarachnoid Injections of Procaine: The Quantitative Effects of Clinical Doses on Sensory, Sympathetic and Motor Nerves, J. A. M. A. **102**:425 (Feb. 10) 1934.

border of the muscle. The muscle is then retracted mesially, exposing the anterior layer of the lumbodorsal fascia, which, when incised, exposes the quadratus lumborum muscle. This muscle is split longitudinally, and the peritoneum is exposed. With a cotton pledget the peritoneum is gently dissected away from the quadratus lumborum muscle until the edge of the psoas major muscle is exposed. The dissection is carried still farther toward the median line, until the vertebral column is encountered, which is usually about the level of the second lumbar vertebra. The crura of the diaphragm are attached to the first and second lumbar vertebrae, so the dissection is turned upward at this point until the crura are exposed. Descending from above downward, between the crura, are the splanchnic nerves. Sometimes they occur singly or fused into one large trunk, and by elevating the perirenal fascia and placing the nerves on tension, 3 or 4 cm. can be resected.

Following this, the dissection can be carried downward and the lumbar sympathetic chain exposed by retracting the psoas muscle laterally. The first and second lumbar sympathetic ganglions can then be resected.

In the majority of cases the postoperative course is uneventful, and the patients are up and about in from six to ten days. The only case in which there was any difficulty following operation was one in which the nerves were small, and in order to be sure that sufficient amounts of them had been resected, the exposure was carried up into the pleura, and a transient pneumothorax complicated the convalescence.

REPORT OF CASES

Case 1.—A man, aged 39, came to the clinic in September 1930 because of high blood pressure that had first been discovered eight years previously. The patient's father had died of hypertension, and one sister had hypertension. Eighteen months before admission the patient had noticed "fulness in the head," dizziness, insomnia, apprehension and daily headaches.

When taken hourly for twenty-four hours, the blood pressure was 185 systolic (mean) and ranged from 150 to 220; the diastolic pressure was 125 (mean) with a range of from 110 to 145. The enlargement of the heart was graded 1, and the sclerosis of the retinal arteries, of the hypertensive type, was of grade 2. Renal insufficiency was not demonstrable. The patient was treated medically by means of rest and sedatives, and his diet was restricted.

The patient returned to the clinic about two years later. During the interval he had taken his own blood pressure from time to time; it revealed a progressive, widely fluctuating, severe type of hypertension. The headaches had persisted, and moderate dyspnea was present on exertion. Hemoptysis had occurred four months previously, and vision had become blurred; the latter condition had lasted from one to six hours. The retinal arteries were examined by Dr. Wagener, who found sclerosis graded 2, generalized retinal spasm, slight edema of the disks and a few hemorrhages and exudates. The systolic blood pressure was 210 (mean) and ranged from 170 to 245; the diastolic pressure was 145 (mean) and ranged from 120 to 180 (fig. 1). The electrocardiogram revealed inversion of the T wave in lead I. There was no renal insufficiency, and there were no formed elements in the urine.

The patient returned a month later for operation. The response of the blood pressure to local application of cold consisted of an increase from 210 to 245 systolic and from 150 to 170 diastolic (fig. 1).

On Oct. 26, 1932, the left major and minor splanchnic nerves and the twelfth thoracic or first lumbar ganglion were resected. The postoperative course was uneventful. Fourteen days after operation, hourly readings revealed that the

systolic blood pressure was 185 (mean), with a range of from 170 to 205; the diastolic blood pressure was 135 (mean), with a range of from 120 to 150. The headaches had entirely disappeared. After fourteen days the patient was walking about; his general condition was satisfactory. There was no change in the appearance of the vessels of the ocular fundi, and the patient was allowed to return home on November 10.

Three months later the patient returned for resection of the right splanchnic nerves. Since his first operation he had been fairly active, but the headaches had recurred in the morning. He had had a severe attack of influenza during this interval, on the second day of which blurring of vision of the left eye had developed and persisted. The retinal arteries were markedly narrowed, with sclerosis graded 2 and 3, recurrence of angiospastic retinitis, fresh cotton-wool hemorrhages and exudates and edema of the disks. Urinalysis revealed the presence of albumin, graded 2, with an occasional hyaline cast. The concentration of urea was 28 and

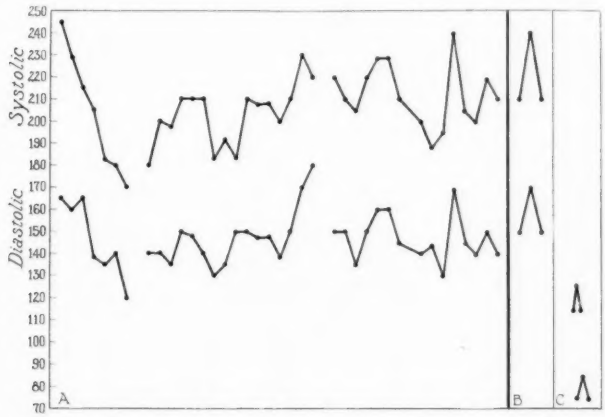

Fig. 1 (case 1).—*A*, hourly systolic and diastolic blood pressures before operation; *B*, response to the application of cold; *C*, results of a cold test in a normal person.

50 mg. in each 100 cc. of blood. In the electrocardiogram the T waves were inverted in leads I, II and III. The blood pressure was 210 systolic (mean) and ranged from 195 to 230; the diastolic pressure was 160 (mean), with a range of from 140 to 180 (fig. 2 *A*). With the cold test the blood pressure increased to 240 systolic.

On Jan. 23, 1933, the right major and minor splanchnic nerves were removed. The right sympathetic cord, at the level of the first lumbar ganglion, also was resected. Observations during operation revealed sharp responses in systolic pressure following manipulation of the splanchnic nerves (fig. 2 *B*). Following resection of the minor splanchnic nerve there was a sharp drop of 40 mm. in the systolic blood pressure, and following resection of the greater splanchnic nerves there was a further drop of 30 mm. to 130 systolic and 105 diastolic. The patient's general condition was satisfactory after the operation. There was no evidence of shock. The blood pressures were taken hourly during the entire postoperative period. At the end of the fifth day the blood pressure had returned to a systolic

mean of 205 and a diastolic mean of 135. At the end of fourteen days the patient was up and about. Determinations of blood pressure when the patient had exercised showed 190 systolic and 135 diastolic. The responses of the blood pressure to stimulation by cold gradually increased from the first to the fourth day and then remained constant (fig. 3). At the time of dismissal there was no significant change in the retinal vessels except thrombosis of a small retinal vein.

Clinically, the patient seemed somewhat improved. The headaches in the morning had disappeared. The value for blood urea was slightly high, and the urine revealed albumin and casts. The function of the gastro-intestinal tract was not disturbed. After his return home the patient was carefully observed by Dr. Crawford of Tulsa, Okla. There was no further drop in blood pressure. There was slight recurrence of the headaches in the morning, and in a letter dated April 27 it was stated that the patient had lost the sight of the left eye. A rather severe degree of hypertension had developed. The patient died in July 1933, probably of renal insufficiency.

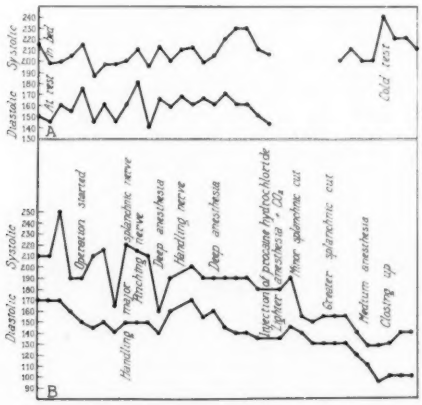

Fig. 2.—*A*, hourly blood pressure and response to the application of cold three months after resection of the left major and minor splanchnic nerves and the twelfth thoracic ganglion; *B*, sharp response in systolic pressure during the operation, with manipulation of the splanchnic nerves. The fundi showed: constriction of the retinal arteries, grade 3; sclerosis, grades 2 and 3; recurrence of angiospastic retinitis; edema, exudates and hemorrhages. There was an inverted T wave in leads I, II and III.

The measurements of the arterioles in a section of muscle removed at operation revealed a ratio of lumen to wall of 1:1.2 as compared with the normal of 1:0.5 (fig. 4). According to Keith's grouping of the organic forms of hypertension, based on examination of the retina and measurements of arterioles, this case would fall in group 3, a borderline group of malignant forms of hypertension.

Comment.—The studies in case 1 are of interest from the physiologic standpoint. The presence of a severe form of hypertension, with marked hypertrophy of the media of the arterioles and other findings, indicated a malignant form of hypertension. The effect of resection of the left

splanchnic nerves revealed moderate reduction in the responses and in the levels of the patient's blood pressure. Several months later an infection which exerted a deleterious effect on the severity of hypertension developed, and mild renal insufficiency, spastic retinitis and significant changes in the electrocardiogram were noted. The second operation was carried out during this phase. Within two weeks there was gradual restoration of the levels of blood pressure and responses to the values before operation. The clinical responses in this case were not encouraging; it seems reasonable to suppose that during this stage the neurogenic factor in the hypertension was of minor importance. The hypertrophic changes in the media of the arterioles and the development of infectious toxemia with the onset of renal injury suggest that peripheral factors became predominant and were the major factors in initiating and main-

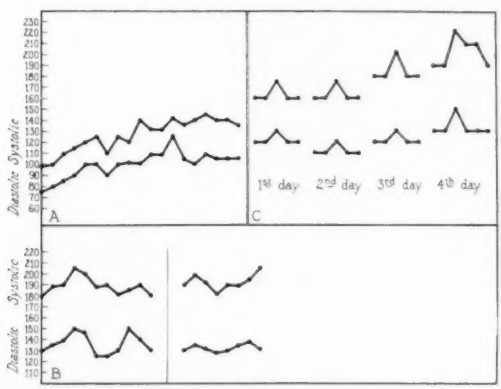

Fig. 3.—Hourly readings of the blood pressure after resection of the right splanchnic nerves: *A*, first day after; *B*, two weeks after; *C*, cold tests following operation.

taining high levels of blood pressure. It seems likely that the renal insufficiency had nullified the depressor effects of the bilateral operation. It is of interest that unilateral resection of the splanchnic nerves did not prevent or apparently change the course of progressive renal disease.

Case 2.—A woman, aged 34, of Syrian ancestry, knew of no family history of hypertension. At the age of 23, when pregnant for the second time, mild toxemia developed, and the systolic blood pressure rose to 200. Following delivery, the blood pressure was 130 systolic, and the patient felt well. A third pregnancy five years later was uneventful. Three years after the third pregnancy the systolic blood pressure was 185 and the patient had headaches in the morning. After that the systolic blood pressure varied between 150 and 200. Seven weeks before admission to the clinic visual disturbances of the right eye developed, with severe occipital headaches and vertigo.

Examination revealed narrowing and sclerosis, graded 1, of the retinal arteries of the hypertensive type. Residual edema and a macular star, the residue of angiospastic retinitis of the right eye, were present.[15] The heart was enlarged to grade 1. Roentgenograms of the thorax revealed diffuse dilatation of the aorta.

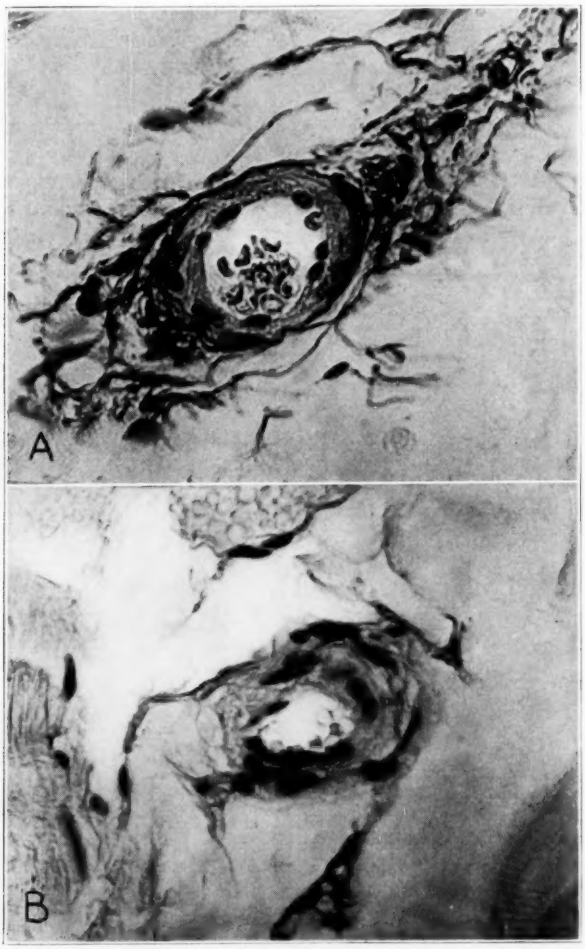

Fig. 4.—Photomicrograph showing the ratio of the arteriolar lumen to the wall: *A*, normal ratio; *B*, ratio in case 1.

15. Wagener, H. P.; Barker, N. W., and Burke, C. F.: Acute Angiospastic Retinitis: Occurrence in Cases of Severe Hypertensive and Renal Disease, Am. J. M. Sc. **185**:517 (April) 1933.

Albumin in the urine was graded 2; there was no impairment of the ability of the kidneys to excrete urine. No significant changes were observed in the electrocardiogram.

Hourly determinations of the blood pressure under controlled conditions for forty-eight hours revealed a mean systolic pressure of 200, with a range of from 160 to 225 and a mean diastolic pressure of 135, with a range of from 120 to 150 (fig. 5). The response to cold was 50 systolic and 30 diastolic, with maximal readings of 230 systolic and 150 diastolic. Spinal anesthesia with 60 mg. of procaine hydrochloride reduced the blood pressure to 140 systolic and 100 diastolic, with a reduction of the response to cold to normal values of 10 systolic and 8 diastolic.

The left major and minor splanchnic nerves were resected on Dec. 1, 1932; in addition, the first lumbar sympathetic ganglion was removed. Manipulation of the splanchnic nerves during operation increased the systolic pressure 50 mm. and the diastolic pressure 30 mm. Sectioning the nerves was followed by a fall of 50 systolic and 30 diastolic (fig. 6).

On the day following the operation the response to cold was 40 systolic and 20 diastolic, with a maximal level of 190 systolic and 130 diastolic. The patient

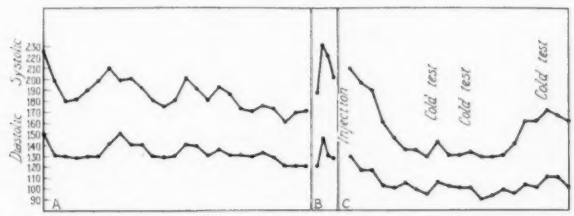

Fig. 5 (case 2).—*A*, hourly determinations of blood pressure during rest; *B*, cold test; *C*, effect of spinal anesthesia (analgesia to the second dorsal segment). The fundi showed: mild angiospastic retinitis; constriction of the retinal arteries with sclerosis, grade 2, and residual edema.

recovered uneventfully and was dismissed on the fourteenth day after operation. Examination of the ocular fundi at the time of dismissal revealed that most of the retinal arteries were of good caliber; sclerosis was graded 2 in the smaller branches, and there was a residual cotton-wool patch in the right disk. The headaches and dizziness had entirely disappeared. Vision had improved. There was no significant change in the blood pressure with changes in posture. The responses to cold were 180 systolic and 120 diastolic.

The patient returned for reexamination three months later. The symptoms were completely relieved. There had been no untoward disturbances in the gastrointestinal or genito-urinary tracts. Menstrual flow had increased in amount. Examination of the ocular fundi revealed that the retinal arteries were of good caliber. Some constriction in smaller branches and few residual exudates were seen. Under stimulation with cold the blood pressure was 40 systolic and 12 diastolic, with a maximum of 206 systolic and 126 diastolic. One year after operation the clinical improvement had remained unchanged.

The clinical condition of the patient was so satisfactory that operation on the right side was deferred.

Comment.—The patient in case 2 had a severe form of essential hypertension, with mild organic changes in the arterioles. Following resection of the left splanchnic nerves, unquestionably the reaction of the blood pressure to cold was lowered, as were the mean levels of blood pressure, which had persisted for three months. Relaxation of the retinal arteries was definite. It is interesting that the operative effects seemed more conclusive following operation on the left splanchnic nerves than on the right, as in case 3. The increase in menstrual flow following operation is of interest.

Case 3.—A woman, aged 33, a nullipara, had known for eight years that she had hypertension. During this period she had been observed from time to time at the clinic; the levels of blood pressure were slowly progressive, the diastolic

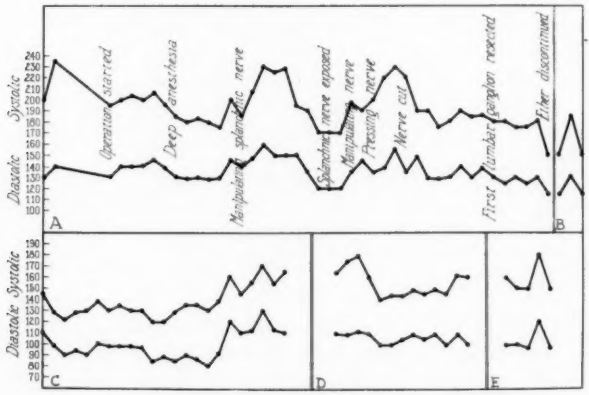

Fig. 6.—*A*, readings of blood pressure during resection of the left splanchnic nerves; *B*, cold test; *C*, pressures on the first day following the operation; *D*, pressures two weeks after the operation; *E*, cold test.

being more marked. The systolic pressure had been moderately labile. In the past few months the patient had had headaches in the morning, progressing dyspnea and general fatigue. The heart was enlarged to grade 2, and there were systolic murmurs in the apical and aortic regions. The specific gravity of the urine was lowered. The concentration of sulphates was 6.1 mg. per hundred cubic centimeters of serum.

Before operation hourly readings of the blood pressure revealed a mean pressure of 200 systolic, with a range of from 160 to 220, and a mean diastolic pressure of 140, with a range of from 120 to 170. The cold test raised the blood pressure to 250 systolic and 170 diastolic; return to the previous level was delayed. The electrocardiogram gave evidence of an inverted T wave in lead III. The retinal arteries were narrowed, graded 2+, with sclerosis, graded 2, of the smaller branches; the retinitis was that of a severe form of hypertension (group 3). The patient could not tolerate spinal anesthesia, and preoperative studies were incomplete.

The right splanchnic nerves were resected on April 1, 1933. The sympathetic trunk was resected, and the first lumbar ganglion was removed. Right pneumothorax developed at the time of operation, and the patient was placed in an oxygen tent; the postoperative period otherwise was uneventful. The general condition was satisfactory, and the patient was dismissed from the hospital on April 17. She was kept under observation.

Twenty-four hours following operation the blood pressure averaged 210 systolic and 160 diastolic. At the time of dismissal the mean blood pressure for twenty-four hours was 220 systolic and 160 diastolic. The systolic pressure varied from 200 to 235; the diastolic pressure, from 150 to 170. Seventeen days after operation, when the patient was up and about, the mean pressure was 195 systolic and 140 diastolic. The response of the blood pressure to cold was unchanged. There were no demonstrable changes in the retinal arterioles.

Six weeks after operation, an infection developed in the upper part of the respiratory tract, from which the patient recovered. A pleural friction rub was noted at this time. The patient gained 8 pounds (3.6 Kg.), and the general condition was excellent. She returned for reexamination on July 3. There were no symptoms except fatigue. In the interval following dismissal several infections of the upper part of the respiratory tract developed. The blood pressure was 235 systolic and 150 diastolic. Albumin, graded 3, and a few erythrocytes were present in the urine. The value for urea was 30 mg., and the return of phenolsulphonphthalein was 35 per cent. The value for sulphates was 8 mg. Examination of the ocular fundi revealed a few fresh hemorrhages and exudates.

On August 22 the blood pressure remained fairly constant (230 systolic and 150 diastolic). With the cold test the pressures were 250 systolic and 170 diastolic. There was a residual pleural rub over the base of the right lung. The retinal findings were unchanged. The patient had gained 14 pounds (6.4 Kg.) and had no symptoms. Eight months after operation, her general course was progressively downward, with evidence of mild renal insufficiency. The blood pressures were unchanged.

Comment.—The patient in case 3 had marked organic change in the retinal arteries and in the specimens of the arterioles removed for biopsy (fig. 7). Following operation there was no reduction in the mean levels or in the response of the blood pressure to stimulation. There was definite stabilization of the blood pressure at rather high levels. Respiratory infection had a serious effect on the kidneys and retinal arteries. The blood pressure increased, the diastolic more than the systolic. The early renal insufficiency had a pressor action, nullifying the possible beneficial effects of the operation. The course of events in this case is similar to that in case 2. A prolonged period of rest and further observation will be carried out before resection of the left splanchnic nerves can be considered.

CASE 4.—A man, aged 34, was first seen in 1921, at which time his blood pressure was normal and his complaints were not related to any form of cardiovascular disease. His second admission was on Dec. 5, 1932, at which time he complained of fulness in the head, more evident in the morning on arising. He was excitable and emotional. With the headaches there was vertigo when he bent over or suddenly turned the body. Following moderate exertion there were definite

dyspnea and palpitation for short periods. The mean blood pressure was 200 systolic and 140 diastolic. Examination of the retinal vessels revealed sclerosis, graded 2, with extensive retinitis of a severe form of hypertension (group 3). The peripheral arteries were hypertrophied and tortuous. Urinalysis revealed the presence of albumin, graded 3, and a few hyaline casts. The value for sulphates was 4.2 mg., and the value for urea, 26 mg. The concentration of hemoglobin was normal, and there was no renal insufficiency. A specimen of muscle removed for biopsy revealed diffuse vascular disease (group 3). Latent glomerulonephritis was considered, but in view of the changes in the arterioles, it was felt that the renal findings were secondary to the nephrosclerosis.

The patient returned to the clinic on June 26, 1933, for reexamination. The symptoms had been practically unchanged except for increased mental irritability. Examination at this time revealed that the blood pressure varied from a basal

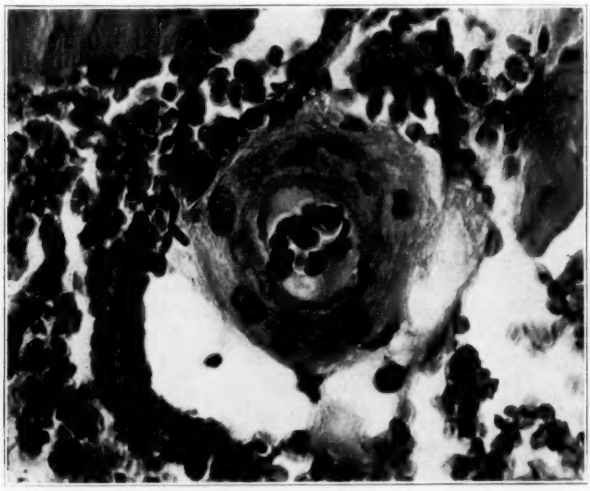

Fig. 7.—Organic changes in an arteriole.

level of 208 systolic and 112 diastolic to 248 systolic and 150 diastolic. The retinitis was still active, and there was irregularly distributed sclerosis, graded 3, of the arterioles with venous dilatation and marked localized periarteritis and endarteritis of the left superior temporal arteriole; partial obliteration was present, and suggested an inflammatory element. There were slight blurring and mild edema of the margins of the disks. These changes indicated the development of a malignant form of hypertension. Urinalysis revealed albumin, graded 3, with fixation of the specific gravity; the value for urea was 38 mg., and that for sulphates was 5.2 mg. An electrocardiogram revealed an inverted T wave in lead I. Physical examination revealed no changes.

Keith and Horton felt that the patient had made some definite progress since his previous visit. The patient asked if operation on the sympathetic nerves would offer him any relief. Spinal anesthesia at the level of the nipple disclosed a residual blood pressure of 170 systolic and 130 diastolic.

In spite of the marked organic change in the vessels and the early renal insufficiency, the wishes of the patient were carried out in this matter, and on July 10 the left splanchnic nerves, twelfth thoracic ganglion and a portion of the sympathetic trunk were resected. Convalescence was uneventful. The pressor responses to cold may be noted in figure 8. There is considerable variability in the maximal levels obtained with stimulation by cold. Thirteen days after operation the patient was up and moderately active; at this time the mean blood pressures were 170 systolic and 120 diastolic. The general condition was satisfactory. The value for blood urea was 56 mg., and for serum sulphates, 6.8 mg. The patient was allowed to return home for several months before it was decided to resect the right splanchnic nerves. At the time of his dismissal, there was no significant change in the retina.

Comment.—The patient in case 4 had a severe form of essential hypertension, with advanced medial hypertrophy of the arterioles and

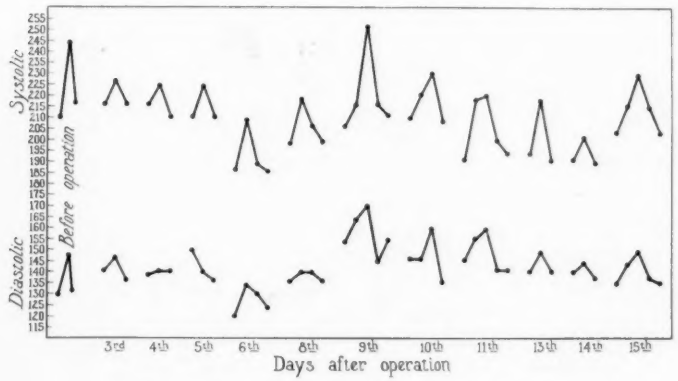

Fig. 8 (case 4).—Pressor responses to cold.

ophthalmoscopic evidence of early malignant hypertension. There was mild renal insufficiency, probably secondary to nephrosclerosis. The basal level of the blood pressure with rest, spinal anesthesia and general anesthesia was 130 diastolic. This patient had a form of hypertension which was not favorable to operation on the sympathetic nerves because of the degree of arteriolar hypertrophy and the added factor of early renal insufficiency, both of which affect the peripheral vasopressor mechanism. The operation was carried out largely at the patient's request, in view of the rather hopeless prognosis; he insisted that we try this procedure.

The response of the blood pressure following operation is of interest. The levels attained by stimulation with cold varied in striking degree, a variation not observed in repeated tests on hypertensive subjects (fig. 8). This variability suggests a peripheral effect, probably from renal toxemia.

Case 5.—A woman, aged 32, did not know of any family history of hypertension. The complaints on admission were arthritis and diffuse neuromuscular pains. The patient was known to have had hypertension for at least eight years. The systolic blood pressure had been found to be as high as 190 and with rest as low as 144. The patient had had frequent attacks of vertigo associated with nausea, and there had been increased fatigue, exhaustion, nervousness and slight dyspnea.

The retinal arteries were found to be attenuated, with sclerosis of the hypertensive type, graded 1. Definite hypertrophy of the heart could not be demonstrated. Urinalysis gave negative results. The value for urea was 22 mg. Hourly studies of the blood pressure under basal conditions revealed a range from 120 to 180 systolic and from 80 to 130 diastolic. The response of the blood pressure to stimulation by cold was 190 systolic and 130 diastolic; following inhalation of 10 per cent carbon dioxide the maximal response of the blood pressure was 195 systolic and 140 diastolic. The diagnosis was essential hypertension in the early organic stage, with marked fluctuations in the responses of the blood pressure to stimulation.

On Aug. 18, 1933, the left splanchnic nerves and the twelfth thoracic and first lumbar sympathetic ganglions were resected. A specimen of the lumbar muscles was removed for biopsy. The patient recovered promptly; she was up and about on the eighth day, and convalescence was uneventful. There was a reduction of

Studies of Temperature (Degrees Centigrade) of the Feet in Case 5

	Sole	1	2	3	4	5
Left	30.3	26.9	26.7	26.7	26.9	27.1
Right	34.7	32.5	33.8	34.1	34.3	34.4

approximately 20 in the systolic pressure reaction to stimulation with cold, and one week after operation the left foot was much warmer than the right. This vasodilatation gradually disappeared, and within two weeks the temperature of this foot reached that of the other.

On September 12 the right splanchnic nerves were resected and the lumbar sympathetic chain was divided; two ganglions were resected. Recovery from this operation was uneventful. The right foot became much warmer than the left, and this persisted until the patient's dismissal a month later. As no symptoms could be attributable directly to the hypertension, there was no particular change in the subjective sensations. The patient stated that there was perhaps slight increased laxity in the movements of the bowels, but there were no other untoward symptoms in the abdominal viscera.

The temperature of the toes one month after operation in degrees centigrade is given in the table.

There was complete absence of sweating of the right leg below the knee and of the left leg below the lower middle part.

Comment.—The patient in case 5 had a fairly early form of essential hypertension; apparently it was just entering the organic phase. The blood pressure was remarkably labile and fluctuated within wide limits. Biopsy, obtained at the time of the first operation revealed questionable thickening of the muscular coat of the arterioles. It is obvious from studies of the blood pressure that the response to the bilateral operation

was not marked. Sharp increases in the patient's blood pressure could be induced with a standard stimulus (cold), but at a somewhat reduced level. The vasodilatation of the feet was incomplete in the left leg and probably complete in the right leg. It persisted for thirty days following the operation on the right side. So far as is known, the same ganglions were removed, the twelfth thoracic and first lumbar. Sweating tests gave further confirmation of incomplete removal of the sympathetic fibers on the left side and complete removal on the right.

THE EFFECTS OF THE OPERATION ON BLOOD PRESSURE

It is difficult to make comparisons of the changes in blood pressure of different subjects because of the differences in the severity of the hypertension. In addition, general anesthesia and the prolonged rest following operation usually lower the levels of blood pressure. For that reason comparison of the preoperative and postoperative readings of blood pressure was considered valid after the patient had resumed activity. Of greater import in our opinion in evaluating the effects of operation has been comparison of the pressor responses of the blood pressure to cold and psychic stimulation.

In case 1 a quantitative effect was demonstrable on the retinal arterioles. Following bilateral resection of the splanchnic nerves, the depressor effects were not significant. For several months following the operation on the left side, the levels of blood pressure were lower, and there was diminished lability in the hourly readings. The course of the hypertension was seriously affected by an intercurrent infection and by the development of renal insufficiency, which led to the patient's death six months later. We believe that the renal condition nullified to a large degree the possible depressor effects of the operation. This patient had the most severe form of hypertension of any patient in this series and the greatest degree of organic change in the arterioles. The effects of changes in posture on the blood pressure were not decisive. No significant lowering of the systolic pressure was obtained in the upright position.

In case 2, in which the left splanchnic nerves were resected, there was moderate reduction in the responses and mean levels of the blood pressure, and these continued to be below the preoperative levels. The hourly fluctuations in the readings of blood pressure were sharply diminished.

In case 3, following resection of the right splanchnic nerves, the only significant effect on the blood pressure was a tendency toward stabilization, but the mean levels, if anything, were higher. Again, an intercurrent infection, which was contracted a month after operation and which was causing renal injury, may have excited pressor effects.

In case 4, following resection of the left splanchnic nerves, the proper reactions to cold were inconstant and variable, a condition not observed in repeated tests on hypertensive subjects. The mean levels were not affected.

In case 5, a fairly early form of hypertension, with marked lability and exaggerated pressor reactions, was noted. Bilateral resection of the splanchnic nerves was followed by a moderate reduction in the height of the pressor responses.

THE POSSIBLE EXPLANATION OF THE LACK OF EFFECT ON THE BLOOD PRESSURE

If significant effects on the blood pressure are not obtained after bilateral resection of the splanchnic nerves, the following explanations seem valid: 1. The splanchnic arteries are not completely denervated. A few preganglionic fibers descend by way of the aorta and are not removed by the operation. In addition, there are some fibers which contribute to the splanchnic enervation from the lower lumbar ganglions; the number and significance of these nerves in man are not known. Cannon [16] stated that in animals they are present in considerable numbers. 2. The vasomotor nerves of the arterioles of the thorax and the upper and lower extremities, which remain after the splanchnic nerves are removed, are sufficient to cause a general vasopressor effect. This seems unlikely, as cervicothoracic and lumbar sympathetic ganglionectomy do not produce significant depressor effects. 3. The organic hypertrophy in the arterioles is too advanced, superimposing a peripheral factor on the central vasopressor control. 4. If renal insufficiency is present, it is likely again that the peripheral mechanism is disturbed, superimposing an added pressor element.

SYMPTOMATIC EFFECTS OF RESECTION OF SPLANCHNIC NERVES

The clinical effects of the operation depend largely on the symptoms attributable to hypertension that existed before operation. In case 1 relief of the patient's headaches was temporary, and their recurrence could be attributed to the subsequent development of renal insufficiency. In case 2 the patient's headaches and vertigo were entirely relieved. In case 3 there were no symptoms that could be attributed directly to the hypertension, in spite of the fact that the patient had a severe form of hypertension. In case 4 the symptoms were those of cerebral irritability, and evaluation of symptomatic effects was difficult. In case 5 the patient had no symptoms which could be attributed to the hypertension.

16. Cannon, Bradford: The Effects of Progressive Sympathectomy on Blood Pressure, Am. J. Physiol. **97**:592 (July) 1931.

COMMENT

The problem of selection of patients for operation is crucial. It is more complex than the selection for sympathetic ganglionectomy of patients with occlusive diseases of the peripheral arteries. In treating a given patient with hypertension, it is desirable to determine preoperatively the probable effects on levels and responses of blood pressure by temporarily blocking the splanchnic nerves.

Under spinal anesthesia to the level of the nipples, small doses of from 60 to 80 mg. of procaine hydrochloride being used, the blood pressure was lowered, and the vasopressor responses of the patients were greatly diminished or obliterated. The abolition of the pressor reactions by this procedure indicates the neurogenic mediation of these reactions. Untoward effects of lowering of the blood pressure are not noted. Spinal anesthesia not only anesthetizes the splanchnic nerves but the lower sympathetic chain and the motor and sensory nerves to the lower extremities and abdominal wall. With spinal anesthesia to levels as high as the nipple, a greater number, and additional types, of nerves are blocked than are blocked by splanchnic sympathectomy.

The degree of organic hypertrophy of the musculature of the arterioles is of great importance in predicting the probable postoperative depressor effects. This can be determined by careful examination of the retinal arterioles and by noting the presence or absence of spastic phenomena. Pathologic study of arterioles of specimens of muscle removed for biopsy gives decisive information as to organic grading and prognostic information. It must be recognized, however, that the degree of changes in the arterioles is not uniform throughout the body, and a too exact deduction cannot be made from the changes in one group of arterioles. We are of the opinion that the following criteria are useful in determining suitability for operation in a case of hypertension: The subject should be less than 45 years of age; the levels and responses in blood pressure should be markedly variable; changes in the smaller arterioles should not be advanced, and severe, degenerative changes should not be present in the kidneys, heart or brain. The foregoing constitute the major requisites for this operation. A basal level of the diastolic blood pressure of not more than 120 is desirable.

Essential hypertension is assumed to be the result primarily of: (1) a hyperreactive vasomotor center with exaggerated pressor responses from psychic, sensory, chemical or hormonal stimulation; (2) consecutive to these excessive, rapidly varying intra-arterial stresses, organic hypertrophy of the arterioles is induced, and (3) in the more advanced stages renal sclerosis and associated vasospastic reactions superimpose an added and more serious element. The two last mentioned conditions are believed to be peripheral; the former, central. Operative measures

which block the central mechanism from the splanchnic circulation should theoretically be effective in the absence of a gravely disturbed peripheral mechanism.

This concept of the various stages in essential hypertension is useful in the interpretation of postoperative results. It emphasizes in which stage of the disease the most striking improvement from operation should be obtained.

Untoward Effects.—There was no significant disturbance of the function of the abdominal viscera that could be attributed to unilateral or bilateral section of the splanchnic nerves. In case 1 severe constipation developed following the second operation. In case 2 there was slight weakness of the right abdominal muscles with a small area of anesthesia in the right lower abdominal quadrant. More exact studies should be carried out on the function of the gastro-intestinal system and especially the effect on renal function following the unilateral operation.

SUMMARY

Five patients with essential hypertension of varying degrees of severity have been subjected to unilateral or bilateral resection of the splanchnic nerves and to removal of the first lumbar ganglion. In two subjects, significant quantitative reduction of the pressor reactions to cold resulted. In one subject, subjective and objective improvement was striking. In the most severe forms of essential hypertension, with early renal involvement and advanced organic changes in the arterioles, the effects on the blood pressure have not been striking. Resection of the splanchnic nerves is a relatively safe operation and carries small risk. No untoward effects have been noted. Further application of this surgical procedure is justifiable in the early stages of the severe progressive form of essential hypertension in young persons.

ALLERGIC DEATH

VII. PROTRACTED SHOCK

GEORGE L. WALDBOTT, M.D.
DETROIT

Reference has been made recently in the literature to instances of sudden death which were thought to be due to physical allergy, particularly to sensitization to cold (Tannhauser,[1] Grassl[2]). Few, if any, reports of allergic deaths induced by the antigenic substances which are commonly encountered in allergic diseases can be found, except deaths which followed parenteral injections of pollen and serum.[3]

Yet the possibility of such deaths is strongly suggested because of the relative frequency and severity of nonfatal generalized reactions following contact with, or the inhalation or ingestion of, antigens, particularly in allergic children. Duke,[4] for instance, described the case of a man who was so sensitive to fish glue that licking a postage stamp produced a severe generalized reaction. He recorded other incidents of similar reactions following skin testing by the scratch method. I have recorded[5] similar observations from both my own experience and that of others.

Evidence has been presented[6] that cases of so-called "thymic death" manifest pathologic changes which appear to be identical with those of allergic shock.[7] An attempt is made here to substantiate the theory of this identity by enlarging on a condition which is frequently encountered in such cases, namely, the occurrence of bronchopneumonic lesions.

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1. Tannhauser, S. J.: Zur Frage des Badetodes, München med. Wchnschr. **79**:1890, 1932.

2. Grassl: Zur Frage des Badetodes, München. med. Wchnschr. **79**:1469, 1932.

3. Waldbott, G. L.: (*a*) Systemic Reactions from Pollen Injections, J. A. M. A. **96**:1848 (May 30) 1931; (*b*) The Prevention of Anaphylactic Shock, ibid. **98**:446 (Feb. 6) 1932.

4. Duke, W. W.: Asthma, Hay Fever, Urticaria and Allied Manifestations, St. Louis, C. V. Mosby Company, 1926.

5. Waldbott, G. L., and Anthony, G. E.: So-Called Thymic Hyperplasia: IV. A Follow-Up Study of Thirty Cases, Am. J. Dis. Child. **47**:34 (Jan.) 1934.

6. Waldbott, G. L.: So-Called "Thymic Death": VI. The Pathologic Process in Thirty-Four Cases, Am. J. Dis. Child. **47**:41 (Jan.) 1934.

7. The term "anaphylactic shock" appears to be more appropriate because the evidence for a distinction of allergic from anaphylactic shock is not conclusive. However, in order to avoid confusion, I am adhering to the terminology of Coca which is accepted at present by most writers.

EXPERIMENTAL EVIDENCE

The phenomenon of "protracted" anaphylactic shock in animals is well known to immunologists. Its manifestations were described by Dean and Webb,[8] who found in their experiments with anaphylaxis in dogs that in the more severe cases of shock which did not terminate fatally there "is another train of symptoms" after the acute state has subsided. This is characterized by dyspnea, fever, diarrhea, stupor, vomiting and general malaise. In guinea-pigs a similar picture was produced by Ratner and his co-workers[9] by means of continued exposure to the antigenic substances after the production of shock. Other workers (Ishioka,[10] Busson,[11] Friedberger,[12] Fried[13]) have spoken of "sterile anaphylactic pneumonia" which occurs in guinea-pigs sensitized to horse serum on insufflation or inhalation of horse serum into the trachea. The lesions which are thus produced may offer the clinical picture of interstitial bronchopneumonia or they may involve whole lobes. Hemorrhagic infarctions of various sizes were noticed among the inflammatory lesions. The aseptic character of the lesions and the presence of lymphocytes and of emphysema are additional features which suggested a pathologic differentiation from true pneumonia.

In man, I have encountered a syndrome corresponding closely with that of protracted anaphylactic shock on three different occasions: first, following injections of antigen; second, in cases of severe asthma, and third, among patients who died of what had been termed "thymic death."

REPORT OF CASES

1. *Protracted Allergic Shock Following Injections.*—CASE 1.—M. B., a 7 year old girl with asthma who was sensitive to various foods, pollen and epidermal allergens was given 0.1 cc. of a 1:100 solution of cotton-seed extract for the purpose of hyposensitization. Within three minutes an area of local edema, the size of an apple, occurred at the site of the injection. This was soon followed by generalized urticaria, edema and severe wheezing. From 0.5 to 1 cc. of epinephrine was given every half hour to an hour to control the reaction. The wheezing and urticaria were held in check for some time, but the child's condition

8. Dean, H. R., and Webb, R. A.: The Morbid Anatomy and Histology of Anaphylaxis in the Dog, J. Path. & Bact. **27**:5, 1924.

9. Ratner, B.; Jackson, H. C., and Gruel, H. L.: Respiratory Anaphylaxis; Sensitization, Shock, Bronchial Asthma and Death Induced in the Guinea-Pig by Nasal Inhalation of Dry Horse Dander, Am. J. Dis. Child. **34**:23 (July) 1927.

10. Ishioka, S.: The Histology of Anaphylactic Pneumonia, Deutsches Arch. f. klin. Med. **107**:500, 1912.

11. Busson, B.: Protein Anaphylaxis Induced Through the Respiratory Passages, Wien. klin. Wchnschr. **24**:1492, 1911.

12. Friedberger, E.: Ueber Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **8**:239, 1910.

13. Fried, B. M.: Allergic Lobar Pneumonia (Experimental Study), J. Exper. Med. **57**:111, 1933.

warranted hospitalization for the balance of the day. When discharged twenty hours after the injection, she was practically free from symptoms. As soon as she returned home, severe wheezing started again, and was followed within a half hour by fever and cyanosis. At that time the chest showed areas of consolidation, bronchial breathing and râles alternating with rhonchi. The temperature ranged between 101 and 103.5 F. This lasted for three days. The removal of a cotton blanket from the child's bed resulted in decided relief from the wheezing. After the symptoms had entirely subsided the patient was retested by the scratch method and by passive transfer for cotton to which she had given a 4 plus reaction before. The skin tests gave a negative reaction at first, changing to a positive reaction seven days later.

CASE 2.—Miss A. M., 18 years old, who had pollen hay fever complicated by clinical sensitivity to horse hair, was given 0.1 cc. of a 1:1,000 solution of horse hair extract as an intradermal test. Within five minutes a marked wheal and local swelling occurred, followed immediately by a generalized reaction. The patient was observed in the office for four hours, during which time she was given small doses of epinephrine. She was relieved for approximately eight hours; then she retired to her bed on which there was a mattress made of horse hair. Immediately a cough and wheezing developed, soon followed by fever, râles and impairment of the percussion note in the chest. On removal of the mattress the wheezing subsided, but the fever, ranging from 100 to 102.5 F., persisted for two more days.

Comment.—In these two cases of severe allergic shock, the symptoms did not subside in the usual way, but were followed by a condition resembling low grade bronchopneumonia. The continued contact with the causative antigen undoubtedly aggravated the condition in a manner similar to that demonstrated in the experiments of Ratner and his associates. Its removal tended to counteract the symptoms of shock, but did not influence the secondary infection. It is noteworthy that negative skin reactions were encountered soon after the shock, in spite of definite previous sensitivity. This corroborates previous observations on skin tests following shock from substances other than pollen and serum (Waldbott[14]). Walzer[15] also recorded negative reactions to skin tests and passive transfer tests in a case of shock following an injection of horse serum.

CASE 3.—M. H., a 12 year old colored girl, was given 0.2 cc. of typhoid vaccine intravenously as treatment for iridocyclitis, on April 6, 1933. There was a history of asthma in the child's family. About four hours after the injection fever, dyspnea and cough developed, followed by unconsciousness and involuntary urination and bowel movements. The temperature was 103 F., the pulse rate 110 and the respiratory rate 30. On the following day the physical signs of bronchopneumonia in both lungs were detected. On the third day following the injection the child died.

14. Waldbott, G. L.: Allergic Shock from Substances Other Than Pollen and Serum, Ann. Int. Med. **7**:1308 (April) 1934.

15. Walzer, M.: New Diagnostic Methods in Asthma, Long Island M. J. **60**: 85, 1932.

The autopsy (Dr. W. R. Prentice, Kalamazoo, Mich.) revealed, on gross examination, slight congestion and edema of the cerebral and meningeal blood vessels and a few petechial hemorrhages in the cerebellum. There were areas of solidification in both lungs; other sections showed extreme congestion and still others marked emphysema. The spleen was enlarged (422 Gm.). There were numerous enlarged lymph nodes, particularly in the gastro-intestinal tract and cervical region. The thymus weighed 22.5 Gm. Otherwise no noteworthy pathologic changes were found. On microscopic examination the brain showed slight congestion, and the lungs were patchy with early bronchopneumonia, with massive intra-alveolar hemorrhages and edema, necrosis of the alveolar epithelium and marked emphysema. There was some cloudy swelling of the hepatic cells with marked congestion in the capsule of Glisson. The thymus, spleen and other lymph nodes were markedly congested and the lymph tissue hyperplastic.

Comment.—While the theory of allergic death caused by a bacterial vaccine may not be fully in accord with the conception of shock from nonbacterial antigens, this case is reported here because the pathologic changes seemed to correspond fully with those reported observed in sensitized animals following injections or inhalation of nonbacterial antigens, and also with my observations at autopsy following "thymic death." Furthermore, the family history in this case suggested that the patient was probably allergic.

I have had occasion to study two other cases of death following intravenous injections of typhoid vaccine which showed the identical clinical course and pathologic changes.

2. *Protracted Shock in Persons with Asthma.*—In a recent paper Clarke [16] described a type of asthma characterized by unusual severity. He mentioned as its symptoms extreme prostration, coma, râles in the lungs and fever. His patients did not improve with the administration of epinephrine. Clarke stated that this condition occurred in few of his patients with asthma. I have encountered this condition in several cases, but in only two was I able to record the full sequence of events.

CASE 4.—Mrs. J. C., 31 years old, had attacks of severe asthma for four years at intervals of three or four months. When she spoke of the attacks she expressed extreme fear, much more than I have seen in any other patient. She had a feeling of impending death. The skin tests showed from 2 to 3 plus reactions to various foods, ragweed, timothy and red top grass, chicken feathers and hair from dogs and cattle. The patient was treated with injections of extracts of chicken feathers and ragweed and autogenous vaccine, from October 1931 to November 1932, during which time she had one slight attack of asthma. In November 1932, a few minutes after she had contact with a dog, a severe attack developed which necessitated hospitalization. There were profuse sweating, a pulse rate of over 140, coma and dyspnea. Numerous râles were heard in various parts of the chest, areas of impairment alternating with areas of hyperresonance. The heart sounds were faint; no murmur was heard. The blood

16. Clarke, J. A.: Status Asthmaticus or Subacute Asthma, J. Allergy **4**: 481 (Nov.) 1933.

pressure ranged about the level of 95 systolic and 50 diastolic. There was expectoration of large quantities of sputum which occasionally showed a bloody tinge. Epinephrine in doses of from 0.5 to 0.75 cc. was of no avail. On the third day the temperature began to rise to about 102 F., as indicated in figure 1. The blood count showed 11,000 white blood cells, with 68 per cent neutrophils, 32 per cent lymphocytes and no eosinophils. During the following days large quantities of thin clear sputum were expectorated. The patient regained consciousness, and the condition in the chest cleared up rapidly. Skin tests done at that time gave negative results; but when repeated two weeks later they showed reactions similar to those previously noted, including a 3 plus reaction to dog hair.

CASE 5.—Mrs. L. K., a 27 year old woman, with severe asthma, who was sensitive to various antigens, took during an interval when free from asthma a patent medicine containing sodium salicylate for the relief of headache. She knew that she was sensitive to this drug, but did not know that it was contained in the medicine. Within a minute she became short of breath. She had scarcely given herself 0.5 cc. of epinephrine when she lost consciousness. One hour later she

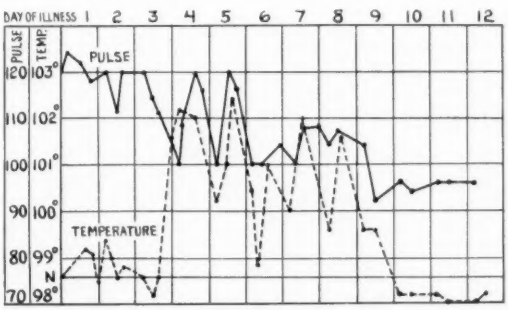

Fig. 1 (case 4).—Pulse and temperature curve in protracted allergic shock.

was found on the floor wheezing severely, comatose and in collapse. She was taken to the hospital where epinephrine was given in frequent doses, but there was no decided improvement. After about six hours fever developed, and blood-tinged sputum was expectorated. There was evidence of pulmonary edema and of a bronchopneumonic process. The patient was treated with epinephrine, digifolin and intravenous injections of dextrose solution, without noticeable response. On the fourth day, the fever, which had not exceeded 102 F., subsided and the patient improved rapidly.

Comment.—The condition in cases 4 and 5 was distinct from bronchial asthma, because there was evidence of pulmonary edema and an ensuing pneumonic process in the lungs. That the edema was not of cardiac origin was evident from the absence of other signs of myocardial insufficiency and from the subsequent absence of cardiac changes. The pulmonary infection, on the other hand, is distinctly different from primary pneumonia because of the unusual onset and course. Both patients were allergic. The onset of the syndrome was definitely

linked with the ingestion of a drug and the contact with a substance to which the patients were sensitive.

3. *So-Called "Thymic Death."*—The noteworthy pathologic changes in the thirty-six cases of so-called "thymic death" referred to in a previous report [6] consisted of capillary congestion, exudation of edematous fluid and extravasation of blood cells into the alveolar tissue, areas of atelectasis alternating with emphysema, petechial hemorrhages, edema in various organs other than the lungs, eosinophilia and hypoplasia of the suprarenal medulla.

In seven of the thirty-six cases and in three additional cases which I have subsequently investigated, in which bronchopneumonia ensued several hours or days after the onset, the clinical course of the disease paralleled closely that encountered in those previously described. In the following two cases the onset of the symptoms was definitely linked with the taking of certain foods.

CASE 6.—S. L., a boy, 1 year old, had been in perfect health except for frequent afebrile nasal catarrh (allergic?). No family history was obtainable, because the child was a foundling. About one week before death he had an afebrile catarrh of the upper respiratory tract from which he recovered within several days. On the morning of the day of death he seemed playful and in good health. The temperature was normal. At 10 o'clock, while drinking a glass of milk, he suddenly became cyanotic and dyspneic and vomited. The cyanosis and dyspnea increased, moist râles were noted in the lungs and signs of consolidation developed. At 3 p. m. the temperature was about 103 F., and at 6 p. m. the child died. The postmortem examination (Dr. L. Parker, Kalamazoo, Mich.) revealed a thymus gland weighing 40 Gm., hyperplasia of the bronchial and mediastinal lymph nodes, dilatation of the capillaries in the lungs, exudation of fluid into the alveoli with extravasation of blood cells, small areas of bronchopneumonic infiltration and areas of emphysema alternating with atelectasis. There was some congestion of the spleen and kidneys. The suprarenal glands were not examined. Other organs, including the heart, were normal.

CASE 7.—L. S., a 3 month old infant of an allergic mother, showed frequent difficulties of respiration and afebrile nasal catarrh. It was noted that when he was given orange juice, he showed severe dyspnea. When 2 months old, he was given a therapeutic dose of roentgen rays because of roentgenographic evidence "of an increased width of the upper mediastinal shadow with a slight lateral deviation of the trachea." One month later after taking some orange juice, the baby became "extremely pale" and dyspneic during his sleep. The father, a physician, noticed râles throughout both lungs. Within a few hours fever developed and the temperature rose to 104 F. Four hours subsequently the baby died. The autopsy revealed marked capillary congestion and edema, areas of mononuclear and neutrophilic infiltration in the lungs, eosinophilia in the spleen, edema in the leptomeninges and petechial hemorrhages in the peritoneum. The weight of the thymic gland was 15 Gm. The lingual and hilar lymph glands were considerably enlarged. The heart was normal.

Comment.—In case 6, unless one considers as a cause of death a mechanical asphyxiation by food which entered the trachea (which

would have been easily detectable at autopsy), one is inclined to assume sensitization to milk as the causative agent, in view of the history of frequent afebrile "colds" which may have been allergic. In case 7, there was a typical history of sensitization to orange juice with a family history of allergy. The syndrome began after the ingestion of orange juice. In both cases a low grade pulmonary infection preceded death.

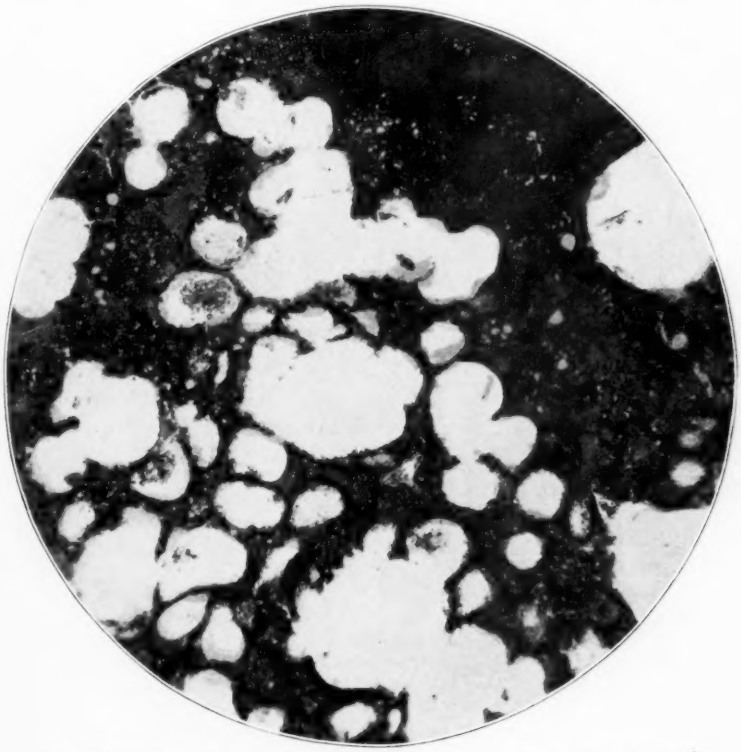

Fig. 2 (case 3).—Photomicrograph of lungs demonstrating hemorrhagic areas.

INTERPRETATION OF OBSERVATIONS

Allergic shock is the result of absorption of an excessive overdose of antigen to which a person is sensitive.[3b] In cases 1, 2, 4 and 5, there is no doubt as to this mode of the reaction. In cases 3, 6 and 7, the allergic background, the course of the clinical manifestations and the parallelism in the pathologic findings with that of allergic shock, on which I have enlarged elsewhere,[6] make it probable that this condition is identical with that of the other cases.

The fever encountered can probably best be explained on the basis of the primary pulmonary edematous hemorrhagic lesions which become infected or infiltrated with cellular elements in an attempt of the organism to organize these lesions. Whether or not bacterial infection plays an essential part in the production of the pneumonic lesions is difficult to say. In view of the presence of edematous hemorrhagic

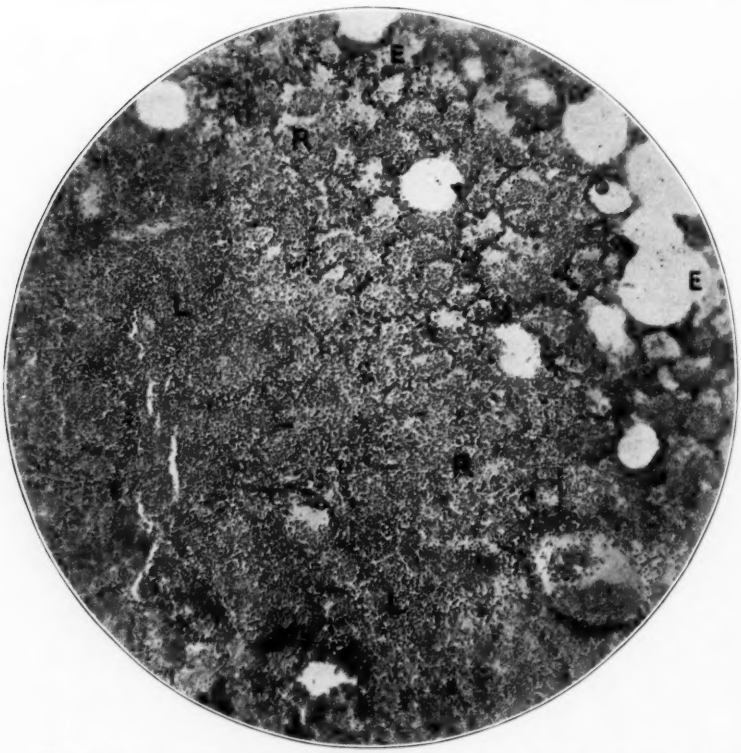

Fig. 3 (case 6).—Photomicrograph of lung demonstrating a hemorrhagic lesion with an adjoining infectious process; *E*, edematous areas; *R*, extravasation of red blood cells, and *L*, leukocytic infiltration.

lesions in the accelerated type of shock, it is likely that in the cases in which bacteria are detected in the blood stream or in the sections of the lungs, one is dealing with secondary infection. Moreover, in most of the tissues examined the infected areas surround the hemorrhagic edematous lesions (fig. 2), which indicates a tendency of the organism to dispose of the primary hemorrhagic lesions.

Of interest in this connection is the case reported by MacDermot [17] of an asthmatic person who had an injection of horse serum and who died several days later. The autopsy showed intra-alveolar hemorrhages, edema and bronchopneumonic areas. MacDermot interpreted the condition as being caused by anaphylactic shock. His microscopic sections, which I had the privilege of examining, show a remarkable resemblance to lesions noted in the cases reported here, particularly to those of case 3.

SUMMARY

The symptom complex of protracted allergic shock is described. It is characterized by a sudden onset of wheezing, dyspnea, shock and the physical findings of pulmonary edema, which is followed after several hours by the development of low grade bronchopneumonia. This has been observed following injections of an overdose of antigen in sensitive persons, in patients with severe asthma following contact with antigens toward which marked sensitivity exists and in ten of thirty-nine cases of so-called "thymic death" which came to autopsy. The detailed reports of two such cases are presented, in which sensitization to food appeared to be instrumental in causing death. The outstanding anatomic changes were edematous hemorrhagic lesions, the border of which showed infectious processes resembling bronchopneumonia.

10 Peterboro Street.

17. MacDermot, H. E.: Pulmonary Intra-Alveolar Hemorrhage in Case of Asthma Associated with Pneumonia, Canad. M. A. J. **22**:533 (April) 1930.

LYMPHEDEMA OF THE EXTREMITIES

CLASSIFICATION, ETIOLOGY AND DIFFERENTIAL DIAGNOSIS: A STUDY OF THREE HUNDRED CASES

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General information about lymphedema tends to be somewhat confused and vague, in spite of a considerable number of excellent reports that may be found in medical literature. This situation is due in large part to the relative rarity of lymphedema, to an inadequate knowledge of its etiology, bacteriology and pathology and to the absence of a comprehensive classification. Although it is impossible for any single author to clarify all these shortcomings, I feel that a presentation of the pertinent data from the records of three hundred cases observed at the Mayo Clinic in the previous ten years offers an opportunity to fill many of the gaps in knowledge and to present a more or less orderly and logical pattern of classification, etiology and description of the condition. Aids to such a presentation are furnished by recent excellent work on the anatomy and physiology of lymph and lymph vessels, well illustrated by a monograph by Drinker and Fields.[1] These facts regarding the anatomy and physiology of lymph vessels and lymph are so important for an understanding of lymphedema that it seems advisable to review them briefly.

DEFINITION OF TERMS

Lymph is a fluid obtained from lymph vessels. Tissue fluid is that found in the region outside blood and lymph capillaries in the cellular interspace. Plasma is the unclotted fluid of the blood. Lymphedema is a swelling of soft tissues due to an increased quantity of lymph. Elephantiasis, an advanced stage of lymphedema, is a "progressive histopathologic state characterized by a chronic inflammatory fibromatosis or hypertrophy of the hypodermal and dermal connective tissue."[2]

ANATOMY

Lymph vessels either are modified veins or arise in situ from mesenchymal cells. They are closed vessels which possess an unbroken endo-

From the Division of Medicine, the Mayo Clinic.

1. Drinker, C. K., and Fields, Madeleine E.: Lymphatics, Lymph and Tissue Fluid, Baltimore, Williams & Wilkins Company, 1933, p. 254.

2. Matas, R.: The Surgical Treatment of Elephantiasis and Elephantoid States, Dependent On Chronic Obstruction of the Lymphatic and Venous Channels, Am. J. Trop. Dis. **1**:60, 1913.

thelial lining, bathed on the outside by tissue fluid. In general, there is more lymphatic than hematic capillary surface. Every main blood vessel has an accompanying lymph vessel.[3] The lymph vessels are as richly supplied with valves as are the veins.[4] India ink injected between two ligatures into the lumen of an artery appears in the lymph vessels around the artery by passing through intracellular stomas and directly through the cells of the arterial wall.[5]

There are a superficial and a deep system of lymph vessels in the leg, but there is no communication between them except through the popliteal and inguinal lymph nodes.[6] In animals most of the superficial lymph vessels of the leg and foot, as well as some of the deep lymph vessels that drain the muscles of the leg, terminate in the popliteal lymph node. From this node large efferent trunks course along the femoral vessels to end in the external iliac nodes, just distal to the bifurcation of the aorta. Many of the superficial lymph vessels of the thigh and upper part of the leg drain into the inguinal lymph nodes, which in turn have efferent vessels terminating in the external iliac nodes. The deeper lymph vessels in the muscle sheaths of the thigh eventually enter trunks that accompany the main femoral lymph vessels, and drain into the large iliac nodes.[7] All the lymph vessels of the leg, both superficial and deep, join at the groin and pass along the external and common iliac vessels through the iliac nodes. The lymphatic trunks at the root of the leg hug the veins closely, and may even be embedded in the adventitia of their walls. They are enclosed in a tough fibrous sheath along with the great blood vessels.[8]

The superficial lymph vessels of the third, fourth and fifth fingers pass to the dorsum of the digits, then upward and around the ulnar side of the forearm to the flexor side of the forearm, where they join those coming from the entire ulnar side of the forearm and pass upward into the axillary nodes, with or without intervention of the cubital lymph node. Those of the index finger and thumb pass upward on the dorsum of these digits, then around the radial side of the forearm to the flexor

3. Polonskaja, R.: Zur Frage der Klappen in den Lymphgefässen der unteren Extremitäten des Menschen, Anat. Anz. **74**:395 (Sept. 30) 1932.

4. Funaoka, Seigo: Der Mechanismus der Lymphbewegung, Arb. a. d. dritten Abt. d. anat. Inst. d. kaiserl. Univ. Kyoto (ser. D) **1**:1, 1930.

5. Iwanow, G.: Die Lymphgefässe der Wände der Blutegefässe—Vasa Lymphatica vasorum sanguinorum, Ztschr. f. Anat. u. Entwicklungsgesch. **99**: 669, 1933.

6. Trout, H. H.: Ulcers Due to Varicose Veins and Lymphatic Blockage; a New Principle in Treatment, Arch. Surg. **18**:2281 (June) 1929.

7. Reichert, F. L.: The Regeneration of Lymphatics, Arch.Surg. **13**:871 (Dec.) 1926.

8. Homans, John: Phlegmasia Alba Dolens and the Relation of the Lymphatics to Thrombophlebitis, Am. Heart J. **7**:415 (April) 1932.

surface, where they join those coming from the radial side of the forearm, and pass upward to the axillary nodes. An occasional lymph vessel may pass upward on the extensor surface of the forearm to well above the elbow, where it turns sharply around the ulnar side of the arm to its inner side and thence to the axillary nodes. The superficial lymph vessels of the arm empty into the axillary nodes or, much less frequently, into the deltoidopectoral or supraclavicular nodes. The deep lymph vessels of the arm run with the large vessels to empty into the axillary lymph nodes, with or without the intervention of the deep cubital lymph nodes. The superficial and deep lymph vessels are connected at the elbow by the deep and superficial cubital lymph nodes.[9]

Regeneration and Collateral Circulation.—If a large lymph vessel is cut, the circulation is carried on by collateral vessels. Later, the passage between the two cut ends regenerates, and the collateral circulation recedes. Collateral lymph vessels develop a few days after ligation of the main trunks.[10] Regeneration of lymph vessels is rapid. They cross the scar of an incision as early as the fourth day, and by the eighth day regeneration is physiologically adequate.[11]

PHYSIOLOGY

The lymphatic endothelium is more permeable than that of hematic capillaries. It possesses no selective absorptive power, but merely admits material forced on its outer surface. Particles of microscopic dimensions deposited in various parts of the body cannot move far except by entering and passing along the lymph vessels.

Pressure and Circulation of Peripheral Lymph.—In amphibians, reptiles and some birds the lymph heart is very important for the movement of lymph. This organ is lacking in mammals. Although the media of the wall of the thoracic duct of man is made up of circular, smooth muscle fibers interlaced with collagen and elastic connective tissue, and although peripheral lymph vessels may have more or less smooth muscle fibers in their walls, it has not been demonstrated that these muscular elements have much to do with the movement of lymph. Active or passive contraction of skeletal muscles plays the most important part in the movement of lymph; the valves of the lymph vessels serve as the most important accessory arrangement for moving lymph forward.[4]

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9. Bartels, Paul: Das Lymphgefäss-System, Jena, Gustav Fischer, 1909, p. 280.

10. Funaoka, Seigo, and Skirakawa, Shigekiyo: Ueber die Entstehung der kollateralen Lymphbahnen nach Ausschaltung des Stammstroms, Arb. a. d. dritten Abt. d. anat. Inst. d. kaiserl. Univ. Kyoto (ser. D) **1**:15, 1930.

11. Reichert, F. L.: The Recognition of Elephantiasis and Elephantoid Conditions by Soft Tissue Roentgenograms, With a Report on the Problem of Experimental Lymphedema, Arch. Surg. **20**:543, (April) 1930.

The speed of circulation of lymph is rapid, but it varies greatly. Trypan blue injected into a lymph vessel of the foot of a dog may reach the receptaculum chyli in ten seconds, and sodium salicylate, injected similarly, can be detected in the lymph of the thoracic duct in one minute and twenty seconds. Bromphenol blue, injected intravenously, appears in the cervical lymph in two and a half minutes.

The flow of lymph is increased by increased functional activity of the part, by increased venous pressure and by general or local hyperthermia, but it is modified little, if any, by peripheral section of nerves and increased arterial pressure. Intravenous injections of solutions may cause increased flow of lymph by effecting a greater movement of water out of blood vessels or by injuring capillary endothelium, thus allowing proteinized fluid from blood to leak into the tissues. Inflammation causes an increased flow of lymph by increasing the blood flow, the venous, capillary and tissue pressure and the capillary permeability, unless the process is severe, when the flow of lymph may be decreased because of occlusion of the lymph vessels by pressure, thrombi, necrotic débris or fibrous tissue.

The pressure of cervical lymph in dogs is from 8 to 18 mm. of a solution of sodium carbonate, the specific gravity of which is 1.08, and in horses from 5 to 20 mm. of the same solution. The lymphatic pressure in the ear of a mouse is from 2 to 4 cm. of water. The pressure in the lymph vessel below the popliteal gland of the resting dog is undiscernible, but it increases to 68 cm. of water after forty minutes of passive exercise. Lymph vessels will stand a surprising amount of pressure without rupture and without serious incompetence of valves. Sterile inflammation may increase peripheral lymphatic pressure to 120 cm. of water.

Constituents of Peripheral Lymph.—The protein in peripheral lymph of dogs varies from 1.84 Gm. per hundred cubic centimeters when at rest to 0.5 Gm. when active. Fibrinogen and prothrombin are present in lymph, but platelets are absent. Leukocytes, of which about 95 per cent are lymphocytes, vary in number from 403 to 68,000 per cubic millimeter. Occasionally, erythrocytes are found when the subject is at rest, and as many as 13,000 per cubic millimeter are present when the subject is active. The carbon dioxide-combining power of lymph is about 50 volumes per cent. The amounts of nonprotein nitrogen, urea, creatinine, sugar and chlorides in lymph are slightly greater than in blood plasma, but the amounts of amino-acids, total phosphorus and calcium are slightly less.

Coagulation of Lymph.—As stated, lymph contains fibrinogen and prothrombin, but it clots more slowly (from ten to twenty minutes) than blood (from four to six minutes), owing to deficiency of thromboplastic

substance ordinarily supplied in a large degree by blood platelets that are absent in lymph. This deficiency is corrected and coagulation of lymph occurs whenever cells in contact with the lymph stream undergo necrosis, or whenever lymph stasis and living bacteria in lymph coexist.[12] When thrombosis of the lymph vessels occurs, the thrombi contract and shrink away from the wall of the vessel, leaving adequate space for the circulation of lymph, except when the coagulating process is progressive. Lymph vessels may be completely filled with thrombi in the region of a phlegmon.

Various foreign substances injected into an area of severe inflammation do not pass into the lymphatic capillaries, but the same substances, when injected intravenously, accumulate rapidly in the inflamed area. Both observations are explained on the basis of thrombosis of the lymph vessels and the presence of a fine network of fibrin which obstructs the flow of lymph away from the inflamed area.

EXPERIMENTAL STUDIES OF LYMPHEDEMA

Lymphedema can be produced by the removal of the lymph hearts in animals. Reichert [11] showed that complete excision of the iliac and inguinal lymph nodes of dogs and cats did not produce edema; even ligation of the iliac or femoral vein added to this procedure was not followed by edema. In further experiments, he divided the limb of a dog transversely, leaving in continuity only a carefully denuded femoral artery and vein; the edges of the wound were then carefully resutured. The resultant edema occurred on the second day, reached its maximum on the fourth or fifth day and subsided completely on the seventh or eighth day. After the eighth day, ligation of the femoral vein caused no recurrence of edema, but occlusion of the lymph vessels by injection of foreign particles caused its reappearance. When excessive scar tissue was produced in the incision in the skin and subcutaneous tissues, the edema remained for ten days or more, and injections of india ink revealed blockage of some of the superficial lymph vessels. These experiments indicate that lymphedema can be produced, but with considerable difficulty, owing, doubtless, to free collateral circulation at the root of the leg, a factor too little emphasized.

Hommans [8] felt that the swelling of the limb in phlegmasia alba dolens could not be explained on the grounds of venous occlusion alone. Experimental ligation of veins of animals did not produce edema, and examination of swollen limbs in patients with phlegmasia alba dolens impressed him with the probability that lymphatic obstruction was an important factor in production of the edema. He ligated the common and internal iliac veins in dogs, injected 5 cc. of a broth culture of

12. Opie, E. L.: Thrombosis and Occlusion of Lymphatics, J. M. Research **29**:131 (Nov.) 1913.

Streptococcus viridans into the femoral vein and ligated it distal to the point of injection.[13] Characteristic phlegmasia alba dolens occurred. India ink was injected into the paws of the edematous legs, and after a suitable time the animals were killed. India ink was found at the level of the lower ligature; from this point to the inguinal ligament there was no pigment, but the common iliac nodes were loaded with particles of ink. Homans concluded that the experimental procedure caused a periphlebitic reaction sufficiently extensive to block temporarily the perivascular lymph vessels of the trunk. He pointed out how suitable the anatomic arrangements for such a condition are; all lymph vessels of the lower limb join at the groin to form trunks which hug the veins closely, and which may even be embedded in the adventitia of their walls.[14] All the vascular trunks, arterial, venous and lymphatic, are closely bound together in a tough, fibrous sheath. From clinical and experimental observations, Homans felt that the cause of phlegmasia alba dolens is obstruction of lymph vessels, but that the basic lesion is always in the common or external iliac vein.

Zimmerman and de Takáts [15] injected a solution of sodium salicylate or tincture of iodine into isolated segments of the common and external iliac veins of dogs, and in some instances sprinkled some of the solution along the outside of the vein. In all animals there was a periphlebitic reaction, even to necrosis of perivenous tissues, but edema did not occur. In further experiments, they dissected the iliac lymph nodes and all the retroperitoneal, fatty and areolar tissues from the bifurcation of the aorta to Poupart's ligament, and from the posterior parietal peritoneum to the psoas muscle. They then ligated and divided the common and internal iliac veins. There was no edema in eight animals, transient edema in two and marked edema in one.

In another experiment, these investigators injected material into the femoral vein of dogs below the point of ligature. Alcohol produced marked edema, but since objections might be raised to the use of it on the basis of the periphlebitic inflammation produced thereby, bland substances were used also. Tissue extract, fibrinogen and barium sulphate in gelatin all produced marked edema when injected into the femoral vein below the point of ligature. Injections of india ink into the footpads of animals with edematous legs indicated that the lymph vessels were permeable.[16]

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13. Homans, John, and Zollinger, Robert: Experimental Thrombophlebitis and Lymphatic Obstruction of the Lower Limb, Arch. Surg. **18**:992 (April) 1929.

14. Homans, John: Thrombophlebitis of the Lower Extremities, Ann. Surg. **87**:641 (May) 1928.

15. Zimmerman, L. M., and de Takáts, Géza: The Mechanism of Thrombophlebitic Edema, Arch. Surg. **23**:937 (Dec.) 1931.

16. Unless a specific reference has been given in the preceding paragraphs, authority is from the monograph of Drinker and Fields.[1]

CLASSIFICATION OF LYMPHEDEMA OF THE EXTREMITIES OF MAN

The cases of lymphedema studied lend themselves to division into two main groups, inflammatory and noninflammatory; the terms infectious and noninfectious could be used as well. The division into the two groups indicates the original state; lymphedema which is originally noninflammatory may be complicated eventually by inflammatory changes. Most cases of lymphedema may be classified without difficulty according to the tabulation.

Noninflammatory Lymphedema.—Primary Lymphedema: "Lymphedema praecox" is an original term applied to a definite clinical syndrome manifested in ninety-three cases in the group studied. It affected female patients predominantly (87 per cent of the cases), and in the majority of instances (65 per cent) had its onset between the ages of 10

Classification of 300 Cases of Lymphedema

	Cases
A. Noninflammatory	
I. Primary	
Praecox	93
Congenital	
1. Simple	12
2. Familial (Milroy's disease)	0
II. Secondary	
Malignant occlusion	32
Surgical removal of lymph nodes	61
Pressure	1
Roentgen and radium therapy	3
B. Inflammatory	
I. Primary (single or recurrent acute and chronic)	41
II. Secondary (single or recurrent acute and chronic)	
Venous stasis	13
Trichophytosis	5
Systemic diseases	5
Local tissue injury or inflammation	34

and 24 years, inclusively. The term "praecox" is used here to denote an early development; in many of the cases in this group the onset of symptoms occurred at puberty, and the incidence of onset in adolescence was impressive.

The swelling occurs spontaneously and without known cause; at the onset, the patient ordinarily notices a puffiness about the foot or ankle. The edema is worse during long periods of activity, during the menses and in warm weather. Rest in bed and elevation of the extremity produce temporary disappearance of the edema that may affect one lower extremity exclusively (70 per cent in this series) or both legs simultaneously, or one extremity may swell months or years after the opposite member has become involved.

The edema ordinarily progresses up the leg slowly, and eventually the entire limb becomes edematous over a period of months or years. The spread of the edema may, however, be much more rapid; the entire limb may be involved within a few days or weeks. In many instances,

swelling is limited to the foot and ankle or does not extend above the knee. Frequently, this particular state is doubtless merely a phase of a progressive condition, but in other instances it seems to represent the maximal degree of extension of the edema.

Gradually the swelling, whatever its limitations, becomes more marked; elevation and rest in bed cause its reduction but not its disappearance. The smooth skin becomes roughened, and the hitherto soft edema becomes resistant to pressure. In addition to enlargement of the limb due to edema, there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly and uncomfortable. A dull, heavy sensation is present, but there is no actual pain.

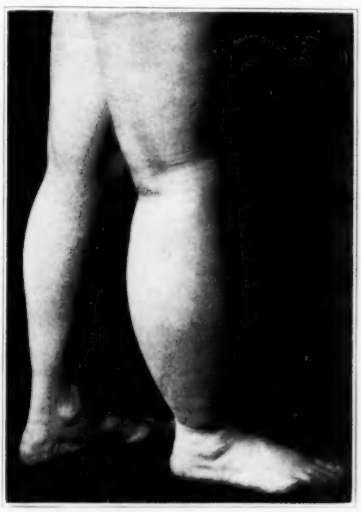

Fig. 1.—Lymphedema praecox in a woman, aged 39 years. Progressive edema of the right leg began at the age of 24 and gradually spread from the ankle to the inguinal ligament.

The entire course of the swelling is ordinarily one of smooth progression; acute lymphangitis and cellulitis occur infrequently (in 13 per cent of the cases studied). Ulceration of the skin does not occur. The entire history is ordinarily that of conversion of a normal limb into a swollen one; nothing else is noteworthy.

The cause of lymphedema praecox is obscure. The predominant incidence among female patients, the onset in the majority of cases during adolescence and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the condition. Possibly the additional load thrown on the lymph vessels by rapidly developing repro-

ductive structures induces a functional incompetence of the lymph vessels or allows entrance of infection into the lymph trunks and nodes in the pelvis. Even minor degrees of functional inadequacy, through obstruction in the pelvis, might lead to dilatation of the lymph vessels below, with incompetence of the valves, particularly among women, whose subcutaneous tissues offer little support. The resulting interference with the free passage of tissue fluid into the lymph vessels provides adequate encouragement for the growth of fibroblasts and further obstruction by connective tissue. While such an explanation of the etiology is highly logical, it is equally theoretical. It is possible that the entire explanation rests on a congenital underdevelopment of lymph

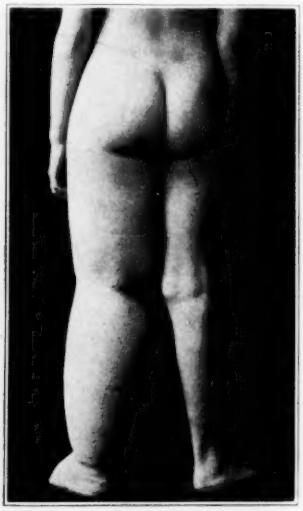

Fig. 2.—Congenital lymphedema in a girl, aged 7 years. Parents noticed the left leg was larger than the right leg on the second day after birth. Enlargement has been progressive since then.

vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities is striking, and it indicates that gravity is an important factor in the development.

Congenital Lymphedema: This may be either simple or familial. In both types, lymphedematous swelling, usually of one lower extremity, is present at birth. There may be actual hypertrophy of the limb, true elephantiasis. In other instances, the skin is soft, and the edema is less resistant to pressure. The two forms do not vary, except that in the

simple type blood relatives are not similarly affected. In the familial type, several persons in the same family have lymphedematous swellings of one or more extremities. The familial type, known as Milroy's disease, was first described as a clinical entity by him in 1892. Milroy [17] said:

Briefly stated, chronic hereditary edema consists in a firm edema. It is limited in extent to the toes or a part or the whole of one or both feet, or of one or both

Fig. 3.—Secondary inflammatory lymphedema in a man, aged 60 years, who was kicked on the tibia by a mule fourteen years previously. The skin was not broken. Eight months later, a sequestrum was removed from the right tibia. No further trouble was experienced until seven years later, when the leg began to enlarge. The swelling was progressive. Roentgenologic examination at the time of admission gave evidence of old osteomyelitis of the tibia.

legs. It never extends above Poupart's ligament. It is not painful or tender and is without constitutional symptoms. It arises from no apparent cause. Hereditary transmission is conspicuous in its behaviour.

17. Milroy, W. F.: Chronic Hereditary Edema: Milroy's Disease, J. A. M. A. **91**:1172 (Oct. 20) 1928.

Milroy's original report was based on a study of six generations of a family of ninety-seven persons, of whom twenty-two had lymphedema; twenty-one of the twenty-two having been born with the condition. Variations from the criteria of Milroy have been so great that the term "Milroy's disease," as used concurrently, is largely without significance. Meige [18] found only eight cases in four generations; the onset at puberty was striking. Hope and French [19] reported thirteen cases among forty-two persons in five generations; in no instance was the condition con-

Fig. 4.—Secondary inflammatory lymphedema associated with trichophytosis in a woman, aged 55 years. A vesicular itching lesion of the skin of the toes, dorsum and plantar surfaces of the left foot had been present for four years. Attacks of acute lymphangitis and cellulitis recurred, and edema had been present for three and one-half years. At the time of examination, trichophytes were found in the cutaneous lesions.

genital; the time of onset ranged from infancy to manhood, and attacks of recurrent cellulitis and lymphangitis occurred. There were no instances of Milroy's disease in this series of cases. Occasionally, a patient stated

18. Meige, Henry, quoted by Milroy.[17]

19. Hope, W. B., and French, Herbert: Persistent Hereditary Edema of the Legs with Acute Exacerbations: Milroy's Disease, Quart. J. Med. **1**:312, 1907.

that he or she believed that a relative was similarly affected with swelling of the extremities, but the details were vague, and in no instance was it proved that the lymphedema was both congenital and familial.

That the criteria of Milroy have been departed from is to be deprecated. Familial lymphedema is not Milroy's disease, according to Milroy's definition, unless the condition is congenital. Many of the cases called "Milroy's disease" are doubtless examples of lymphedema praecox with a familial predilection. The marked hereditary and congenital features present in Milroy's cases have not been equaled in cases reported by others; the situation recorded by Milroy may be unique. This constitutes further reason for close adherence to the diagnostic criteria given. Congenital lymphedema is produced largely by lymphangiectasis, a developmental anomaly.

Secondary Lymphedema: This may be due to malignant occlusion of lymph vessels by metastasis to adjacent lymph nodes of malignant disease of the breast, uterine cervix, uterus, vulva, prostate gland, bladder, testes, skin or bones. Such a possibility serves to emphasize the necessity of close scrutiny for evidence of malignant disease in all cases of lymphedema, since swelling may be the first outward manifestation. Pressure outside the lymphatic trunks perhaps occasionally, but rarely, produces lymphedema. The one case found in this series seemed to follow the use of a truss for inguinal hernia. Secondary, noninflammatory lymphedema may occur in cases of Hodgkin's disease or lymphosarcoma, or may follow surgical removal of lymph nodes and lymph vessels for malignant disease distally situated, or for tuberculosis or metastasis of malignant disease. The last named condition is the elephantiasis chirurgica of Halsted.[20] Such a condition is not uncommonly seen following radical amputation of the breast and axillary lymph nodes for carcinoma. The lymphedema may occur with or without intervention of attacks of lymphangitis and cellulitis. The irregular interval at which lymphedema occurs after radical amputation of the breast is remarkable. Usually the arm begins to swell on resumption of activity, but weeks, months or even years may pass before the extremity becomes edematous. In one instance, the arm was free from swelling for nine and a half years; there was no evidence of the recurrence of malignancy to account for the edema; cellulitis and lymphangitis had not occurred. In such instances, it is possible that fibrosis may be induced by repeated irradiation, thus producing lymphatic obstruction, or that occult lymphedema over a period of years has resulted in overgrowth of connective tissue and obvious edema. Unfortunately, there are no experimental

20. Halsted, W. S.: The Swelling of the Arm After Operations for Cancer of the Breast: Elephantiasis Chirurgica, Cause and Treatment, Bull. Johns Hopkins Hosp. **32**:309 (Oct.) 1921.

data to explain the occurrence of edema after radical removal of the breast; experiments on animals reveal that extensive removal of lymph nodes does not cause edema. Why, then, does this condition occur in man after extensive removal of lymph nodes? Halsted believed it was caused by infection following operation, either obvious or so slight as to avoid detection, or by recurrent attacks of cellulitis and lymphangitis. The question cannot be answered here. The answer may be inherent in the comparatively small number of experiments on animals; lymphedema has not been demonstrated in these experiments, but neither does it occur in many instances following radical removal of the breast in man. If larger numbers of animals were observed over greater periods of time following surgical removal of lymph nodes, it is probable that lymphedema would be noted. The conclusion based on clinical observation cannot be avoided; surgical removal of or metastasis to lymph nodes may produce lymphedema.

Lymphedema may occur after treatment with radium and roentgen rays. Whether such a result is brought about by the fibrosis caused by radiation, or by metastasis of the malignant disease for which radiation is given, cannot be determined with certainty. Barker [21] described a case in which radium irradiation for a disease, apparently incorrectly diagnosed as carcinoma of the uterine cervix, was followed by lymphedema.

Inflammatory Lymphedema.—General Characteristics: The advanced stage of inflammatory lymphedema has been called "elephantiasis nostras streptogenes." All examples of inflammatory lymphedema, exclusive of the chronic form, have one feature in common, single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the praecox type is striking; in the former, progression is by a series of attacks which are impressive in the suddenness of onset, and striking in the severity of systemic reaction; in the latter, the history is one of slowly progressive edema. The usual victim of an attack of cellulitis and lymphangitis of an advanced grade is suddenly seized with a severe chill unpreceded by other symptoms, or, following a short period of distress in the extremity or proximal lymph nodes, his teeth chatter, the bed shakes and he becomes nauseated and vomits. His temperature is between 101 and 106 F.; in a short time a small, reddened area spreads until a considerable portion of the extremity is swollen, red, hot and tender. The proximal lymph nodes are tender and swollen. The chills recur during a period of thirty minutes to an hour. The high fever persists for a period ranging from a few hours to two or three days, and is accompanied by marked malaise that may persist after the temperature returns to normal. The

21. Barker, N. W.: Personal communication to the author.

abnormal condition of the extremity recedes slowly over a period of from four to fourteen days but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus.[2]

Single attacks leave minor degrees of lymphedema, but successive attacks, which tend to occur progressively, more frequently produce increasing edema; each attack is a step toward the final stage, namely, marked lymphedema and elephantiasis. The chronic form of lymphangitis of the spontaneous type is exceedingly rare. In such instances, the leg is persistently warmer than its companion member, and a reddish discoloration of the skin exists. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis. The infection in such instances is considered to be subclinical. It should be emphasized that lymphangitis, whatever its nature, produces occlusion of lymph vessels by thrombosis or by the proliferation of connective tissue.

Primary Lymphedema: This term signifies a condition resulting from single or recurring acute attacks of chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In many such instances, the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis. In other instances, it may be due to infections introduced into the lymph vessels through minor portals of entry unnoticed by the patient. The acute attacks of lymphangitis and cellulitis have been described; each attack leaves a residue of increased edema. In the chronic form of lymphangitis, the edema is slowly progressive.

Secondary Lymphedema: This term indicates a condition resulting from lymphangitis secondary to known causes. The lymphangitis may occur in single or recurrent attacks or in a chronic form. Chronic edema of venous origin may predispose to recurrent attacks of acute cellulitis and lymphangitis, and thus to progressive lymphedema, but such instances are uncommon, in light of the rather common occurrence of thrombophlebitis resulting in edema.

Trichophytosis about the toes may induce recurrent attacks of acute lymphangitis. The inflammation and the resultant edema are ordinarily limited to the foot and ankle. It is probable that an etiologic relationship exists in but a small percentage of instances in which trichophytosis and acute attacks of lymphangitis occur in the same patient. It is not clear whether the trichophytes themselves or secondary bacterial invaders are responsible, even when the trichophytic infection seems to be definitely related to the acute inflammatory attacks. Instances which strongly sug-

gest that the trichophytes are directly or indirectly responsible for the acute attacks are those in which marked evidence of trichophytic infections, such as desquamation and the occurrence of vesicles, precede the appearance of cellulitis and lymphangitis. Pregnancy and systemic diseases such as influenza, typhoid fever, pneumonia, malaria and filariasis may lead to recurrent attacks of cellulitis and lymphangitis and result in lymphedema. Except in cases of filariasis, it is possible that the original lesion is thrombophlebitis that produces venous stasis, subsequent attacks of lymphangitis and, eventually, lymphedema. Occasionally, conversion into the lymphedematous state proceeds without the intervention of attacks of acute inflammation; in such instances, it is assumed that a condition of chronic lymphangitis exists, or that the lymph vessels become obstructed by overgrowth of connective tissue which is, in turn, a reaction to stasis of tissue fluid. Tissue fluid acts as an excellent culture medium; fibroblasts grow and fibrosis results unless the blood plasma is promptly returned to tubes lined with endothelium.[1] It is worthy of note that filariasis was not demonstrated in any of the cases of lymphedema reported in this study. Clinical evidence of, or an antecedent history suggestive of, filariasis was consistently absent; in many instances, blood drawn from the patient at night was studied, but Filaria was never found. It is possible, if not probable, that filariasis existed in some of the cases reported, for it has been shown that failure to find Filaria does not exclude filariasis. The patients of the Mayo Clinic are drawn largely from northern climates where filariasis exists sporadically, if at all, and it is obvious that the absence of this condition as a cause of lymphedema would not hold in more southern locations where filariasis is common.

Local inflammation or injury of tissue leads to the production of lymphedema most commonly through the intermediation of single or recurrent attacks of lymphangitis or chronic lymphangitis. In the cases studied, such diverse causes as contusions, lacerations, surgical incisions, vesicles, abscesses, furuncles, burns, fractures, penetrating wounds, dog-bites, tularemic abscesses, pelvic inflammatory diseases and appendicitis were directly responsible. The acute attacks may occur weeks or months after the original trauma, which may not be associated with any marked clinical evidence of infection. The organisms in the tissues appear to be in a "resting state;" then, for some unknown reason, marked activity occurs, and an acute attack of cellulitis and lymphangitis is clinically apparent. It seems strange that minor abrasions should allow entrance of infection into the tissues, but Hadock and McMaster [22] showed that

22. Hadock, S. S., and McMaster, P. D.: The Lymphatic Participation in Human Cutaneous Phenomena: A Study of the Minute Lymphatics of the Living Skin, J. Exper. Med. **57**:751 (May) 1933.

the slightest wound of the corium may tear lymph vessels open and permit material to enter them directly. In many instances, the lymphedema occurred following injury or infection without the intervention of acute attacks of inflammation, and seemed to be due to a chronic or subclinical inflammation and thrombosis of lymph vessels or to a residue of inflammation from the original injury or infection.

DIFFERENTIAL DIAGNOSIS

There is rarely any difficulty in distinguishing advanced lymphedema, that is, elephantiasis, from edema due to other causes. The brawny indurated skin and the hypertrophied limb of elephantiasis bear little resemblance to manifestations of edema in other diseases. It is only when the lymphedema is not associated with changes in the appearance and feel of the skin that difficulty arises. Lymphedema can be distinguished without difficulty from the edema of general systemic diseases, such as myxedema, myocardial failure, nephrosis, nephritis or deficient proteinemia, when it is unilateral; when it is bilateral, a thorough examination is necessary to exclude these diseases. Sarcomas, lipomas and neoplasms of the bone are almost uniformly unilateral, and they produce regional or localized swellings, whereas the edema of lymphatic obstruction is more uniform and extensive. When swelling of an extremity is localized, careful roentgenologic studies are invaluable from a diagnostic standpoint. Angioneurotic and cyclic edemas are characterized by this intermittence, whereas lymphedema is more constant and disappears during the early phase only on elevation of the limb; well advanced lymphedema responds to this procedure incompletely. Enlargement of a limb in arteriovenous fistula is associated with dilatation of and increased pressure in the regional veins; analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood. If the arteriovenous fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference. All these signs of arteriovenous fistula, except the increased circumference of the limb, are absent in lymphedema.

The edema of limbs occasionally noted in lymphosarcoma is probably of lymphatic origin, but recognition of the basic condition is important. Ordinarily, in cases of lymphosarcoma, there are enlarged nodes in the regions in which nodes are usually palpable, and in the mediastinum. Microscopic examination of a node removed surgically is invaluable when doubt exists. It may be remarked parenthetically that it is always important to examine patients with lymphedema carefully for evidence of malignancy. Lipodystrophy, characterized by "fat legs," is to be distinguished from lymphedema. Young women and girls with lipo-

dystrophy are subject to worry, anxiety and even to embarrassment at the supposed cosmetic disfiguration. Such reactions have arisen largely as a result of short dresses and hosiery advertisements, for aside from a slight disturbance in the symmetry of the body, no disfiguration exists. The condition, however, is as important as it appears to the patients. The characteristic symptoms which lymphedema and lipodystrophy may have in common are predilection for women, similarity in appearance, painlessness and additional swelling of the feet or ankles when patients are on their feet much, particularly in warm weather. Lipodystrophy is uniformly bilateral, and is usually associated with generalized obesity or obesity about the pelvis. The degree, but not the extent, of lipodystrophy may progress after it is first noted. In contrast, lymphedema is usually unilateral, is not ordinarily associated with obesity and usually progresses from the foot proximally, except when it is congenital. Attacks of lymphangitis and cellulitis may occur in lymphedema but not in lipodystrophy. Pitting on pressure may occur in both conditions, but it is less evident in lipodystrophy. The diminution in size, which may follow elevation of the extremities in both conditions, is more marked in lymphedema.

The edema of deep thrombophlebitis is usually to be distinguished from lymphedema because the former is similar to lymphedema in so many respects. Well advanced stages of either condition offer little difficulty in diagnosis. The hypertrophied limb, with the thickened skin and firm consistency, characteristic of elephantiasis, has little similarity to the limb in cases of deep thrombophlebitis, for the latter is marked by softer edema, stasis ulcers, dermatitis and superficial varices. To be sure, when attacks of recurrent lymphangitis or cellulitis occur, the leg that was originally edematous from venous obstruction acquires an additional element of lymphedema, and lymphedema may occur around varicose ulcers as a result of chronic infection. So far as I am aware, however, pure uncomplicated lymphedema, whatever its origin, does not lead to ulceration. It is in the earlier phases of the two diseases that difficulty is encountered; the usual similarity of symptoms includes unilaterality, pitting on pressure, normal skin texture and disappearance of edema following elevation of the limb. Dissimilarities exist in the circumstances of origin, speed of onset and progress, distress experienced by the patient and condition of the superficial veins. Thrombophlebitis with edema usually occurs in the course of or following an illness such as pneumonia or typhoid fever, or follows childbirth or operation. During the acute stage, a dull aching distress occurs in the area of the involved vein, which is tender to pressure; the edema develops rapidly to its fullest extent in the course of hours, and the superficial veins are dilated. Lymphedema does not ordinarily occur during systemic disease. The

absence of distress is striking, except when acute cellulitis and lymphangitis occur; the edema ordinarily develops to its fullest extent slowly over a period of weeks, months or years, and the superficial veins are not dilated. Among dissimilarities, the localized distress that occurs in thrombophlebitis is most important. Occasionally, the two conditions may coexist, as in the case of the thrombophlebitic limb that is involved in recurrent attacks of lymphangitis and cellulitis. In rare instances it may be difficult, if not impossible, to distinguish between the two conditions, although roentgenologic studies may be of some value.[11] The difficulty is particularly great when patients can relate only vague details about the development of the edema.

COMMENT

It is apparent that too little is known about lymphedema. In a study such as the one presented, much depends on the accuracy and details of the clinical history and examination of the patients. Invariably, when the study of patients with any specific condition has been carried out by diagnosticians having diverse interests, too much emphasis has been placed on diagnosis and too little on details of the history and the manifestations of the illness. My study suffers from this difficulty, which is offset somewhat by the fact that in recent years the study of lymphedema at the Mayo Clinic has been centralized. It is only by concentrated inquiry that minutiae of development can be traced in a consecutive manner, and it is only when this is done that facts about the evolution of lymphedema can be arranged in an orderly pattern.

The experimental data on lymphedema are, to say the least, confusing and somewhat contradictory, and at best are inadequate and almost inconsequential with respect to their worth in interpreting clinical phenomena. A condition simulating chronic lymphedema in man has not been produced in animals, and the experimental procedures so far executed appear insufficient when compared with those utilized in the production of venous edema.[23] Mechanical methods for interrupting the flow of lymph at the root of the leg should be, a priori, as devoid of results as those for mechanically interrupting the flow of venous blood. It is not surprising that resection of the pelvic and inguinal lymph vessels does not produce lymphedema, when it is considered that multiple ligations of veins in the same area do not produce venous edema. Experiments corollary to those producing venous thrombosis with venous

23. Since this article was written a report of the experimental production of lymphedema by progressively occluding lymphatic vessels has been published (Drinker, C. K.; Field, Madeleine E., and Homans, John: The Experimental Production of Lymphedema and Elephantiasis as a Result of Lymphatic Obstruction, Am. J. Physiol. **108**:509 [June] 1934).

edema are necessary, namely, lymphatic thrombosis. Too little is known about the collateral circulation of lymph at the juncture of the extremity and the body. Although it is valuable to point out that all lymph vessels join at the groin and axilla and pass along the large blood vessels, it is important to know about the connection of lymph vessels below these regions with the lymph vessels of the abdominal and thoracic walls and of the back. Inasmuch as collateral circulation of the venous blood may be carried on by collateral channels from the root of the limb to the trunk, it is probable that an analogous situation exists for lymph vessels; at least, the analogy between veins and lymph vessels holds in every other important regard.

Even the clinical diagnosis of lymphedema is sometimes uncertain, a situation best illustrated by the equivocal parts played by lymphatic and venous obstruction in phlegmasia alba dolens. This situation is due to the absence of conclusive tests for lymphatic obstruction. Solution of the problem of distinguishing lymphedema from other types of edema may be found in analysis of the fluid in the edematous areas, in tests for speed of circulation of lymph in the extremities or in some method of visualization of the lymph vessels with dyes or by roentgen studies. I feel that the experimental production of chronic lymphedema would be an important step in the solution.

Finally, too little is known about the bacteriologic and pathologic changes in lymphedematous extremities. The etiology and the mechanism of production of lymphedema cannot be fully considered without the information gained from careful study of the pathologic changes and the bacteria involved.

I have pointed out some of the gaps in the knowledge of lymphedema in order to stress the need for further investigation, and to explain why it is impossible to present a completed picture of the disease. I feel that the shortcomings noted should encourage rather than discourage the investigator of lymphedema; the problems that remain unanswered are so important that any progress will be noteworthy.

SUMMARY

The important facts regarding lymph vessels and lymph are reviewed. A classification of lymphedema, based on a study of three hundred cases, is presented. Descriptions are given of the various types of lymphedema, and the mechanism of production is reviewed. Differential diagnosis of lymphatic edema and other types of edema is considered. The shortcomings in the knowledge of lymphedema are mentioned.

CARCINOMATOUS ENDARTERITIS OF THE PULMONARY VESSELS RESULTING IN FAILURE OF THE RIGHT VENTRICLE

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Hypertension of the pulmonary circulation with hypertrophy and consequent failure of the right ventricle is most frequently due to mitral stenosis or to chronic bronchitis and emphysema of long duration. The rôle of these mechanical causes of hypertension of the lesser circulation has been recently reemphasized by Moschcowitz.[1] In a group of cases described by Eppinger and Wagner [2] and by others (MacCallum [3]) as primary sclerosis of the pulmonary vessels, the etiology of the vascular lesion is largely unknown. There is, however, a rather uncommon group in which diffuse metastatic carcinomatous lymphangitis is associated with widespread obliterative endarteritis of the pulmonary vessels. The widespread obliterative endarteritis causes a generalized narrowing of the pulmonary circulation followed by right ventricular hypertrophy and finally right ventricular cardiac failure.

In 1874, Troisier [4] described an interesting clinical picture in patients with carcinomatous lymphangitis of the lungs secondary to carcinoma of the stomach. In describing his cases he commented on the paucity of the physical signs of disease in the lungs. He was concerned primarily with a description of the lymphatic spread of the process and made no mention of the presence of any vascular changes. In the same year, Raynaud [5] and Hillairet [6] published reports of similar cases. They also

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1. Moschcowitz, E.: Hypertension of the Pulmonary Circulation, Am. J. M. Sc. **174**:388, 1927.

2. Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. f. inn. Med. **1**:83, 1920.

3. MacCallum, W. G.: Obliterative Pulmonary Arteriosclerosis, Bull. Johns Hopkins Hosp. **49**:37, 1931.

4. Troisier: Cancer de l'estomac; Cancer secondaire des poumons. Lymphangite pulmonaire généralisée, Bull. Soc. anat. de Paris **48**:834, 1873; Recherches sur la lymphangite pulmonaire, Thèse de Paris, no. 142, 1874.

5. Raynaud, M.: Lecture d'une memoire sur l'angioleucite généralisée des poumons, Bull. et mém. Soc. méd. de hôp. de Paris **11**:66, 1874.

6. Hillairet, M.: Observations d'angioleucite pulmonaire dans le cancer de l'estomac, Bull. et mém. Soc. méd. de hôp. de Paris **11**:78, 1874.

stressed the involvement of the lymph vessels within the lung and pleura, but did not state whether the blood vessels revealed any pathologic changes. Girode, in 1889,[7] was the first to mention the occurrence of endarteritis of the pulmonary arteries in lymphangitis carcinomatosa, but he considered the involvement of the lymphatics by carcinoma to be the important pathologic change.

Girode was aware of the fact that metastases to the lungs could occur by direct extension via the hepatic veins or vena cava system and give rise to pulmonary emboli. However, he believed that the most frequent route for pulmonary metastases was by way of the thoracic duct with a retrograde spread to the cervicomediastinal lymph nodes and to the pulmonary lymphatics, a view in which Bard [8] later concurred.

The French authors were of the opinion that the clinical picture of dyspnea, cyanosis and cardiac failure was the direct result of the pulmonary lymphangitis carcinomatosa, and that vascular changes need not be present. They believed that the compression effects of carcinomatous lymphangitis on the bronchioles and alveoli were adequate to explain the clinical findings.

In 1897, Schmidt [9] reported the finding of tumor cells from a carcinoma of the stomach in branches of the pulmonary arteries. He pointed out that narrowing and obliteration of the pulmonary arterioles were responsible for the hypertrophy of the right ventricle in his case. Later, in 1903, he published a monograph [10] on the modes of metastasis of carcinoma. The occurrence of hypertrophy of the right ventricle was noted in one case of metastatic carcinoma of the lung. In this study, forty-one cases of carcinoma originating in abdominal viscera were examined, in twenty-eight of which there were metastases to the lungs. Of these, fifteen showed carcinoma cell emboli in the pulmonary arterioles without any macroscopic alterations in the parenchyma of the lung. The stomach was the site of the primary growth in seven of the fifteen cases.

Schmidt believed that these tumor emboli spread into the pulmonary vessels via the thoracic duct, the right subclavian vein, the superior vena cava and the right side of the heart, and thence into the pulmonary arterioles. According to him, many of the tumor cell emboli acquire a platelet deposit during their passage through the blood stream. After the emboli lodge in the arterioles, the thrombotic deposit increases by the

7. Girode, J.: Lymphangite cancéreuse pluro-pulmonaire sans cancer du poumon, Arch. gén. de méd. **1**:50, 1889.

8. Bard, L.: La lymphangite pulmonaire cancéreuse généralisée, Semaine méd. **26**:145, 1906.

9. Schmidt, M. B.: Ueber Krebszellenembolien in den Lungenarterien, Verhandl. d. deutsch. naturforsch., Braunschweig, 1897, no. 15, p. 11.

10. Schmidt, M. B.: Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarcome zu den leukaemischen Neubildungen, Jena, G. Fischer, 1903.

further apposition of blood elements. Subsequently the tumor cells disintegrate, the thrombotic material becomes organized, and there results either total fibrous obliteration of the lumen of the vessel or the formation of a pillow-like projection into the lumen of the vessels. Schmidt pointed out that sometimes a secondary deposit of new thrombotic material or of new carcinoma cells occurs on an old fibrosed plaque, after which one may observe within the same arteriole vascular changes of different stages which are easily distinguishable from one another (fig. 1).

Fig. 1.—Carcinomatous endarteritis of a small artery showing recanalization with recent thrombus formation.

Except for the report by Bard [8] in 1906, and an occasional mention of this condition in some of the German textbooks on pathology, no further mention of this condition was made until the publication by von Meyenburg [11] in 1919 and that of Ceelen [12] in 1920.

While the French writers deserve the credit for recognizing the gross pathologic changes in carcinomatous lymphangitis of the lungs and for

11. von Meyenburg, H.: Zur Kenntnis der Lymphangitis carcinomatosa in Lungen und Pleura, Cor.-Bl. f. schweiz. Aerzte **49**:1668, 1919.

12. Ceelen, W.: Ueber einem Fall von Thrombendarteriitis pulmonis carcinomatosa, Med. Klin. **16**:94, 1920.

the observation that the tachypnea and cyanosis are out of proportion to the physical signs in the lungs, the striking histopathologic picture was first described by Schmidt twenty-three years after Troisier's report, and the clinical picture was described in detail by von Meyenburg and Ceelen. The characteristic syndrome is therefore well established in the French [13] and German literature, but it has not been reported in the English or American publications. The following cases are therefore described in order to call attention to the condition.

REPORT OF CASES

CASE 1.—L. K., a white woman, aged 40, was admitted to Mount Sinai Hospital (service of Dr. B. S. Oppenheimer) on Aug. 22, 1929. The family history was irrelevant.

A cholecystectomy and an appendectomy had been performed seven years previously, and an exploratory laparotomy for symptoms of peptic ulcer four years ago. Eleven weeks prior to admission a nonproductive cough developed which was accompanied by a dull pain in the chest and by frequent night-sweats. The cough became increasingly troublesome, and five weeks after its onset dyspnea, progressively increasing weakness and hoarseness developed. Four weeks later the patient was awakened from sleep by a choking sensation in the chest followed by a brief syncope. That night she had three similar attacks of suffocation. These episodes recurred frequently after that time.

One year prior to admission the patient discovered a small mass in the right breast which was painless to palpation. A similar painless mass was felt in the opposite breast. Both masses had enlarged rapidly during the last month. There was no history of hemoptysis, chills or fever.

Physical Examination.—The patient was chronically ill, moderately emaciated and dyspneic and coughed frequently. There was a congenital bilateral internal strabismus. A small lymph node was palpated on the right side of the neck. In the outer quadrant of each breast, firm, hard, nodular masses which were not fixed to the skin or deeper structures were noted. Except for the presence of a moderate number of moist râles, there was a distinct paucity of physical signs in the lungs. The heart was not enlarged. There was a systolic murmur over the pulmonic area. Radial pulses were small in volume but equal. No masses were felt in the abdomen. Several small lymph nodes and one large one were found in the right axilla; in the left axilla there were several small nodes. The lymph nodes were freely movable and not stony hard.

Laboratory Examination.—Studies of the blood revealed: hemoglobin, 60 per cent; red cells, 5,000,000; white cells, 13,000; polymorphonuclear leukocytes, 78 per cent; lymphocytes, 16 per cent; monocytes, 4 per cent, and basophils, 2 per cent. The systolic blood pressure was 82 and the diastolic, 68. The Wassermann reaction of the blood was negative. On admission, chemical examination of the blood revealed 19 mg. of blood urea per hundred cubic centimeters.

Diagnosis.—A diagnosis of chronic bilateral cystic mastitis was made; the possibility of a malignant change in the tumors of the breasts and of pulmonary metastases was considered.

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13. A report in the Presse médicale (**41**:745 [May 10] 1933) by A. Costedoat entitled "La lymphangite cancéreuse des poumons" came to my attention after this paper had been prepared for publication.

Course.—Throughout the patient's stay in the hospital, the temperature remained about 100 F. The dyspnea, which was strikingly apparent on admission, became increasingly conspicuous.

The first night in the hospital the patient was suddenly awakened from sleep by coughing. She felt faint but did not lose consciousness. She perspired profusely, and it was noted that the lips became deeply cyanotic. The pulse became imperceptible for about one minute, and then the rate increased to 104 per minute and remained irregular and weak. During this period the respirations were rapid and somewhat shallow; the rate, however, was not recorded. The "attack" lasted about ten minutes, after which the patient slept comfortably for the remainder of the night. The following day she had a similar attack, except that she lost consciousness for about one minute. These attacks recurred frequently. She was constantly troubled by the dry, raspy cough which had been present on admission.

Three days after admission, Dr. Harry Wessler reported that the roentgen picture of the chest was very suggestive of "lymphangitis carcinomatosa."

The persistent tachypnea (from 30 to 35 per minute) without orthopnea or cyanosis raised the question of acidosis as a possible cause of the rapid respiratory rate. However, the carbon dioxide-combining power of the blood was reported to be 39 volumes per cent. A biopsy, performed on a supraclavicular lymph node four days after admission, was reported by Dr. Paul Klemperer to show "metastasis of a signet ring cell carcinoma with excessive fibroplastic tendencies."

Electrocardiographic tracings one day before death were reported to show "right axis deviation; T_2 and T_3 showed cove-plane inversion."

Under observation, symptoms and signs of failure of the right side of the heart rapidly developed; cyanosis appeared; the liver gradually enlarged; a right hydrothorax and then a small amount of ascites developed.

Embryocardia appeared one day before death. The diagnosis of carcinomatosis of the heart was suggested before death to explain the picture of progressive myocardial failure from which the patient died six days after her entrance to the hospital.

Autopsy.—The essential changes found at postmortem examination are summarized.

Macroscopic Examination: Externally, there was marked cyanosis of the face, lips, ears and nail beds. Each breast contained a firm mass approximately 8 by 4 cm. These masses, which were in the upper and outer quadrant, were not adherent to the underlying skin and did not involve the nipple. Section of the masses in the breast revealed a firm, white, almost cartilaginous tissue that suggested carcinoma.

Both pleural cavities contained a small amount of clear straw-colored fluid. The lungs were free from adhesions. Except for distended, white, prominent lymphatic vessels, the pleurae were smooth and glistening. The lungs weighed 1,280 Gm. The pleural lymphatics were prominent, thickened and infiltrated by a white tissue which formed a cordlike tracery over the surface of the lungs. The lungs were subcrepitant. Numerous pinpoint to pinhead sized nodules were palpated throughout both lungs. On section, it appeared as if all the lymphatic channels were thickened and contained firm white tissue. The intervening lung was grayish brown. There were several anthracotic lymph nodes, which on section revealed an infiltration of firm, white tissue. The branches of the pulmonary arteries presented scattered areas of atheroma. The pulmonary veins presented no gross changes.

The heart weighed 400 Gm. The pericardium contained a slightly increased amount of straw-colored fluid. The pericardial surfaces were smooth and glisten-

ing throughout. The apex of the heart was composed of both ventricles. The right side of the heart was markedly enlarged, owing mainly to a hypertrophied and slightly dilated right ventricle. The valves and endocardium were grossly normal. The left auricle and ventricle showed no significant changes. The aorta presented occasional scattered atheromatous plaques. The coronary arteries were patent throughout and not narrowed.

The liver weighed 1,475 Gm. It was firm and reddish brown. On section, the normal architecture was greatly disturbed and completely replaced by irregular areas of yellow regenerating hepatic tissue interspersed with reddish portions forming a mosaic picture typical of a "nutmeg liver." The hepatic veins were markedly dilated, and the central veins deeply congested. The portal vein and biliary passages were grossly normal.

There was a large, flat, firm tumor located on the lesser curvature about 5 cm. below the esophagus extending to within 4 cm. of the pylorus. On section, this tumor was seen to be composed of a diffusely infiltrating, grayish-white tissue causing a marked thickening of the wall of the stomach and presenting several superficial small ulcerations. Lymph nodes along the curvature of the stomach were markedly enlarged and infiltrated by grayish-white tumor tissue.

Microscopic Examination: The histologic picture of the neoplasm of the stomach was characteristic of a scirrhous adenocarcinoma.

The pleura was thickened, owing to an increase in connective tissue, and contained a moderate sprinkling of lymphocytes, plasma cells and an occasional polymorphonuclear leukocyte. The pleural lymph spaces contained nests of tumor cells, some of which were of the "signet ring" variety. Frequent mitoses in the tumor cells were encountered. Occasionally single carcinoma cells were seen in the tissue spaces.

The connective tissue septums containing the large and small bronchi and vessels were greatly thickened. The septums were made up of richly vascularized connective tissue in which a dense infiltration of lymphocytes, plasma cells and polymorphonuclear leukocytes was seen.

The alveoli near the septums were frequently collapsed, while others were emphysematous. The alveoli contained a small amount of edema fluid, some desquamated alveolar epithelium and a few iron-containing macrophages.

The large arteries possessed a markedly hyperplastic intima which consisted of a thick layer of fibers in the subendothelial region, while the outer portions were formed by a loose interlacing network of connective tissue fibers containing a few fine elastic fibers. The media presented a mucoid change of the ground substance. The adventitia was trabeculated and thickened.

The small arteries of the 2 mm. size frequently presented a narrowed or at times a completely obliterated lumen. The obliteration or the narrowing of the lumen, which was more often eccentric than concentric, was brought about by a loose connective tissue proliferation of the intima. Serial sections revealed that the lumens of these arteries were compromised to various degrees along the course of the artery; in places the narrowing was the result of a plaquelike lesion encroaching on the lumen of the vessel (fig. 2). Frequently an obturating thrombus of fibrin, often containing a single or many carcinoma cells, was found in the lumen of a narrowed artery. The media of these vessels was greatly compressed. The adventitia was difficult to distinguish from the dense and increased perivascular connective tissue which was often edematous and was infiltrated by many plasma cells, lymphocytes and a few polymorphonuclear leukocytes. The perivascular lymph vessels contained large nests of tumor cells.

A growth of carcinoma cells into the outer walls of an artery, extending into the lumen, was not observed in this case. The veins showed no changes.

In summarizing this case, a scirrhous carcinoma of the stomach with pronounced metastases to the lymph channels is reported. Both lungs showed diffuse involvement of the lymph vessels by carcinoma. Marked proliferation of the intrapulmonary connective tissue septums with an inflammatory reaction was present. The arterioles, especially the smallest, showed a severe intimal proliferation which in many instances resulted in a complete obliteration of the lumen. The obliteration was at times caused by plugs of fibrin which frequently contained carcinoma cells.

Fig. 2.—An arterial lumen encroached on by an intimal "plaque"; note the infiltration of the media by carcinoma cells.

An attempt to establish conclusively the etiology of the intimal proliferation from the histologic picture is difficult. However, one might assume that the same fibroplastic factor that is responsible for the extensive increase in the perivascular connective tissue might also be responsible for the intimal hyperplasia. In any event, there was no evidence present to indicate an obliteration of the lumen by carcinoma cell proliferation. The single carcinoma cell emboli which were embedded in the plugs of fibrin also cannot satisfactorily explain the diffuse spread of obliterative endarteritis.

The tumor masses in the breasts revealed a histologic picture similar to that seen in the primary tumor of the stomach.

Anatomic Diagnosis.—The diagnosis was infiltrating scirrhous carcinoma of the stomach (linitis plastica) with metastases to both breasts, skin, ovaries, lungs and tracheobronchial lymph nodes; lymphangitis carcinomatosa of the lungs and obliterative endarteritis of smaller arteries and the arterioles; hypertrophy and dilatation of the right ventricle; chronic passive congestion of the liver; fibromyomas of the uterus, and cystic endocervicitis.

Summary.—A white woman, aged 40, presented a history of a dry, nonproductive cough, frequent night-sweats and later dyspnea and weakness.

Examination revealed masses in both breasts, small intracutaneous nodules over the middle of the clavicle and a moderate number of moist râles in the chest.

The clinical course was characterized by rapidly increasing tachypnea and cyanosis terminating in failure of the right ventricle.

The electrocardiographic tracings indicated a right ventricular hypertrophy; the roentgen picture of the chest was suggestive of lymphangitis carcinomatosa.

At autopsy, a scirrhous carcinoma of the stomach was found with lymphangitis carcinomatosa of the lungs and an obliterative endarteritis of the pulmonary vessels.

CASE 2.—J. L., a man, aged 38, was admitted to the Mount Sinai Hospital (service of Dr. Leo Kessel) on April 12, 1932. The past history was unimportant.

The patient stated that he was well until one year before. About that time occasional attacks of localized pain developed in the lower portion of the abdomen which subsequently shifted to the left lower quadrant, with radiation to the epigastrium. The pain was mild and occurred from one to two hours after eating, being relieved somewhat by food and alkalis, but mainly by vomiting. After roentgen examination of the gastro-intestinal tract, the patient was informed by his physician that he had a stenosing peptic ulcer and was placed on a bland diet and advised to use alkalis. With dietary precautions he was symptom-free for about seven months, until three weeks before his admission to the hospital. A feeling of fulness in the upper portion of the abdomen and vomiting after meals developed, and the patient complained of marked anorexia. His symptoms became progressively worse; a week later he began to cough and expectorated about an ounce of mucopurulent sputum daily. Shortly after the onset of the cough, he became dyspneic. At first his dyspnea was mild, but it gradually became so severe that at the time of admission to the hospital it was his most prominent symptom, even while at rest. There had been a loss of 25 pounds (11.3 Kg.) in weight in the last eight months.

Physical Examination.—The patient was robust, slightly obese and dyspneic. There was a distinct pallor of the skin and mucous membranes, but no cyanosis or edema. The veins in the neck were not distended. The chest was barrel-shaped. No dilated veins were noted over the wall of the chest. There was diminution of pulmonary resonance below the angles of the scapulas where the breath sounds were increased in expiration, and occasional crackling râles could be heard. The bases of both lungs moved freely. The heart was not enlarged, the sounds were of good quality, rhythm was regular and no murmurs were heard. The aortic second sound was louder than the pulmonic second sound. The abdomen was markedly distended, particularly in the epigastric region where direct and rebound tenderness was noted. The liver was palpated three and a half finger-breadths below the right subcostal margin. There was no peripheral edema or clubbing of the fingers or toes.

Laboratory Examination.—Studies of the blood revealed a hemoglobin of 69 per cent; 9,000 white cells per cubic millimeter; 82 per cent polymorphonuclear leukocytes, and 14 per cent lymphocytes. The blood pressure was 94 systolic and 70

diastolic. The Wassermann reaction of the blood was negative. Chemical examination of the blood revealed 18 mg. of urea per hundred cubic centimeters, 515 mg. of chlorides and a carbon dioxide-combining power of the plasma of 48 volumes per cent. Examination of the urine gave negative results. The guaiac test for occult blood in the stool was negative. The Rehfuss test meal revealed a total acidity of 44 with a free acidity of 25 only after the administration of 0.5 mg. of histamine, subcutaneously. Gastric aspiration yielded 20 cc. of yellow nonbloody fluid. The electrocardiographic tracings showed a tendency to right ventricular preponderance with the R and T waves low in all leads.

Diagnosis.—A diagnosis of peptic ulcer with pyloric stenosis was made; carcinoma of the stomach was to be excluded.

Course.—In the ward, the patient's temperature fluctuated between 100 and 102 F., with a pulse rate of about 86 and a respiratory rate between 20 and 24 per minute. Roentgenologically, the pulmonary fields were clear; there was marked elevation of the diaphragm on both sides with a resultant upward displacement of the heart. A series of roentgenograms of the gastro-intestinal region was reported as showing no abnormalities.

Four days after admission, signs of congestion appeared at the base of both lungs with presacral edema and ascites. Dyspnea became more marked and was soon accompanied by orthopnea and deepening cyanosis, which was greatly exaggerated by effort. The liver grew larger, and generalized edema became apparent. With these and the electrocardiographic evidence of right ventricular preponderance, it was felt that progressive failure of the right side of the heart due to a myocardial lesion was responsible for the clinical picture, although the exact nature of the cardiac lesion was not known. Another suggestion offered for the circulatory failure was that the failure was due to some mechanical obstruction to the great veins obstructing the return of the venous blood to the heart.

Eight days after admission, the patient became psychotic and extremely cyanotic and died in circulatory collapse.

Autopsy.—The body was that of a well nourished man in incomplete rigor mortis. There was slight pretibial edema. The peritoneal cavity contained about 1,500 cc. of straw-colored fluid.

Each pleural cavity contained approximately 300 cc. of straw-colored fluid. The visceral pleurae of both lungs presented numerous yellowish-white distended lymphatic vessels. On the diaphragmatic surface of the lower lobe of the right lung and in the middle lobe were several small, firm, dark blue areas. The lungs were moderately voluminous and generally crepitant except for a small area occupying the upper lobe of the right lung. On section, the lungs were red and congested and presented a faint brownish tint. The upper lobe of the right lung was fleshy, and much frothy fluid exuded from the lower lobe. The small, firm, dark blue areas were wedge-shaped and represented infarcts. Throughout both lungs, but most marked in the lower lobes, were numerous grayish-white, pinpoint to pinhead sized nodules which caused the lungs to feel finely nodular. The smaller septums stood out as prominent gray strands. The pulmonary arteries showed an occasional atheromatous plaque. In the middle lobe an adherent reddish thrombus occluded the lumen of a medium-sized vein. The bronchial mucosa was reddened. Both lungs presented the same gross anatomic picture.

The pericardial sac contained about 200 cc. of straw-colored, clear fluid. The heart was flabby and small. The right ventricle was moderately dilated and distinctly hypertrophied. The left ventricle was not hypertrophied. The valves and endocardium were normal.

The liver was moderately enlarged and firm and presented a smooth capsule with rounded edges. On section, a variegated appearance was seen, such as is seen in the "nutmeg" liver of chronic passive congestion.

An indurated, flat, smooth, grayish-white plaque with scalloped edges measuring 6 cm. in diameter was seen on the lesser curvature of the stomach about 5 cm. from the pyloric ring. On sectioning the plaque, firm, homogeneous, grayish-white carcinomatous tissue about 5 mm. thick was found. The gastro-hepatic ligament for a distance of about 10 cm. was indurated and diffusely infiltrated. The regional lymph nodes did not appear to be grossly involved.

Microscopic Examination: The histologic picture of the tumor of the stomach was typical of a scirrhous adenocarcinoma.

The lymph vessels surrounding the large and smaller arterial branches frequently contained masses of tumor cells. The perivascular connective tissue was distinctly increased. It consisted of thickened nuclear-poor connective tissue which was infiltrated in the periphery by many lymphocytes and few polymorphonuclear leukocytes. The adventitia merged into the perivascular connective tissue mantle from which it could not be differentiated. The media of some of the smaller arteries was definitely narrowed, but showed no other changes. Many of the smaller arteries showed a marked intimal proliferation which narrowed the lumen of many of the vessels and caused a complete obliteration in others. The intimal proliferation was not always circumferential but was mostly localized and resulted in plaquelike lesions. The elastic interna of these vessels was distinct and not lamellated. The thickened intima consisted of nuclear-poor connective fibers which were interspersed with frequent fine elastic fibers. Occasionally, the narrowed lumen of one of the vessels was further occluded by a plug of fibrin. Tumor cells were not present in the lumen of the vessel in this case.

In résumé, this is a case of a scirrhous carcinoma of the stomach with metastases to the regional lymph nodes and infiltration into the gastro-hepatic ligament and pancreas.

There was marked plugging of the perivascular lymphatics of the lung with carcinoma cells and marked perivascular fibrosis with an inflammatory cellular infiltration. The intima of many arteries showed a definite thickening, often resulting in complete obliteration of the lumen. Plugs of fibrin were present within the lumen of the vessel although no tumor cell emboli were found.

In this case the fibroplastic stimulation resulting in the marked intimal proliferation, often leading to complete obliteration, might also be ascribed to the presence of the carcinoma cells in the perivascular lymph channels, as carcinoma cell emboli are not seen here.

Anatomic Diagnosis.—The diagnosis was scirrhous adenocarcinoma of the stomach with metastasis to the regional and peripancreatic lymph nodes, gastro-hepatic ligament and pancreas; lymphangitis carcinomatosa of both lungs with thrombo-endarteritis of the smaller pulmonary arteries and the arterioles; hypertrophy and dilatation (moderate) of the right ventricle; chronic passive congestion of the liver ("nutmeg"), spleen and kidneys; anasarca (ascites, hydrothorax, hydropericardium, edema of the lower extremities and sacrum); acute pulmonary edema; pulmonary infarcts of the middle and lower lobes of the right lung, and thrombosis of the pulmonary vein of the middle lobe.

Summary.—A white man, aged 38, presented a one year history of epigastric pain, occurring from one to two hours after eating, loss of weight and a three week history of anorexia and vomiting after meals, followed two weeks later by cough and dyspnea.

Examination revealed a dyspneic, anemic-looking man. Pulmonary resonance was diminished below the scapular angles, where an occasional crackling râle could be heard.

In this case, the progressive right ventricular failure greatly overshadowed the gastro-intestinal symptoms. The roentgen examinations both of the gastro-intestinal tract and of the chest gave negative results. The electrocardiographic tracings indicated a tendency to right ventricular preponderance.

At autopsy, a scirrhous adenocarcinoma of the stomach was present, with metastases to the lungs in the form of widespread lymphangitis carcinomatosa of the lungs with a diffuse obliterating endarteritis of the small arteries and the arterioles.

CASE 3.—O. H., a white man, aged 40, was admitted to the medical service of Dr. George Baehr on April 14, 1931. For the past ten years he had experienced vague epigastric discomfort, mild anorexia, headache and occasional vomiting. Two and one-half months before admission he became markedly constipated and occasionally complained of severe pain in the upper abdominal region which usually appeared from fifteen to thirty minutes after eating. Weakness and loss of weight followed the onset of the intestinal disturbance. Two months later a nonproductive cough developed. About this time asthenia became so marked that he had to go to bed. His weight had decreased from 130 to 105 pounds (59 to 47.6 Kg.) in the past two and one-half months.

Examination revealed a chronically ill, wasted man. There were a few crepitant râles at the bases of both lungs. The heart was not enlarged; there were no murmurs. The pulmonic second sound was accentuated, split and louder than the aortic second sound. The abdomen was generally distended. A questionable mass descending with respiration was palpated in the left hypochondrium. No clubbing of the fingers or toes and no edema or cyanosis were found.

Laboratory Examination.—Studies of the blood revealed a hemoglobin content of 78 per cent with 7,600 white cells. The differential count revealed 81 per cent polymorphonuclear leukocytes, 11 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophilic leukocytes. The blood pressure was 128 systolic and 72 diastolic. The Rehfuss test meal showed the absence of free hydrochloric acid in the gastric content; each specimen aspirated was grossly bloody. The stool was reported to contain occult blood. The urinary findings were not significant. Sigmoidoscopic examination gave negative results. Roentgen examination of the colon with an enema of barium sulphate showed only a marked depression of the midportion of the transverse colon with some constriction in this region which was interpreted as "suggestive of adhesions." Roentgen examination of the chest showed a diffuse mottling of both lungs which was considered to be due either to an artefact resulting from the roentgen technic or to developing tuberculosis. The Wassermann reaction of the blood was negative.

Diagnosis.—A diagnosis of an intra-abdominal malignant condition was made.

Course.—Except for increasing restlessness, the patient's course was uneventful until four days after admission, when he suddenly went into collapse without cyanosis. His pulse suddenly rose to 150 per minute, with a respiratory rate of 54 per minute. The temperature was 101.4 F. The patient complained of marked weakness, faintness, dizziness and thirst. The blood pressure reading was 80 systolic and 70 diastolic. Examination revealed that the mucous membranes were pale and the skin cold and moist. The pulmonary fields were clear, and except for tachycardia examination of the heart gave essentially negative results. The hemoglobin was unchanged. Two hours later the patient "appeared very restless,

apprehensive, almost gasping for breath." At this time physical examination gave the same results as it had earlier in the evening. Rectal examination revealed no blood or tarry stool on the examiner's glove. As the hemoglobin was still 78 per cent, hemorrhage was considered unlikely. The patient died one hour later, four days after admission.

Autopsy.—The essential changes found at postmortem examination are summarized. The lungs presented a similar appearance. The pleurae were studded with numerous tiny white nodules. In places there were whitish-gray branching streaks outlining the lymphatic vessels. On section, the lungs were congested and everywhere studded with sharply defined, tiny white nodules the size of a millet-seed. In places the lymphatics appeared like tiny twigs. The tracheal and bronchial lymph nodes were considerably enlarged, and on section revealed tumor tissue.

The heart was not enlarged. The valves, endocardium and myocardium presented no gross abnormalities. The coronary arteries were normal.

There was a moderate amount of free fluid in the abdominal cavity. The omentum was rolled up and firm and contained numerous white, firm tumor nodules. There was a deposit of neoplastic tissue partly lining the culdesac. A firm nodular mass in the wall of the stomach was densely adherent to the peritoneal structures.

The liver was moderately enlarged and congested.

The capsule of the spleen was covered with numerous small metastatic nodules. The hilus was densely adherent to the stomach and the head of the pancreas and was encased in a neoplastic mass.

The pancreas was completely surrounded by neoplastic tissue which infiltrated the substance in some areas. The splenic and mesenteric vessels were not compressed or infiltrated.

Along the entire lesser curvature of the stomach a flat, ulcerated, neoplastic mass was found. This tumor infiltrated the entire posterior wall of the stomach, producing a diffuse thickening and presenting the appearance of linitis plastica. All the regional lymph nodes extending to the porta hepatis, the peripancreatic nodes and the periaortic nodes, which encased the aorta without compressing it, were enlarged by metastases. The inferior vena cava was not involved, and the thoracic duct was lost in the neoplastic tissue, but no tumor tissue was seen within it; grossly, the lumen appeared intact.

Microscopic Examination.—The gastric neoplasm was a scirrhous adenocarcinoma of the stomach, presenting the picture of linitis plastica.

Throughout the lungs the perivascular connective tissue septums were thickened. The perivascular lymph vessels were distended with masses of tumor cells. At times single tumor cells could be seen within the tissue spaces. Frequent mitoses were present. The connective tissue surrounding the blood vessels showed marked infiltration of polymorphonuclear leukocytes and lymphocytes. Frequently an arterial wall was found to be penetrated by tumor cells and presented a polymorphonuclear leukocytic infiltration. The lumen of the great majority of the small arteries and the arterioles contained adherent masses of tumor cells showing frequent mitoses. Frequently the tumor cells were enmeshed in a fibrin plug which partially or completely closed the lumen. Occasionally, early organization of one of these plugs was seen. Often the lumen of these vessels was narrowed or completely obliterated by a connective tissue proliferation of the intima which was infiltrated by polymorphonuclear leukocytes and single tumor cells.

In this case a scirrhous adenocarcinoma of the stomach with extensive metastases to the lymph nodes, liver and peritoneum was present. The lungs showed a

widespread filling of the septums, lymph channels and spaces by tumor cells and a connective tissue proliferation with a diffuse inflammatory reaction. The walls of the small arteries and the arterioles were frequently infiltrated by tumor cells which often plugged the lumens of these vessels and presented numerous mitoses. Some of the lumens were closed by tumor-fibrin thrombi, while others presented an obliterating intimal proliferation infiltrated by polymorphonuclear leukocytes and tumor cells. In this case the genesis of the obliterating endarteritis might be ascribed to infiltration around and into the vessel causing a marked fibroplastic stimulus and not, as Schmidt believed, to multiple carcinomatous emboli. It is still questionable whether the carcinoma masses in the lumen of the vessel could not be explained by an autochtonic proliferation of tumor cells which had penetrated into the lumen.

The veins did not show any significant changes.

Anatomic Diagnosis.—The diagnosis was scirrhous adenocarcinoma of the stomach with metastases to the regional and tracheobronchial lymph nodes, lungs, pancreas, liver and capsule of the spleen; lymphangitis carcinomatosa of the lungs and obliterating endarteritis of the smaller pulmonary arteries and arterioles.

Summary.—A white man, aged 40, presented a two and a half month history of increasing constipation and occasional spontaneous pain in the upper abdominal region followed by weakness and loss of weight. Two weeks before admission a nonproductive cough developed. Examination revealed a chronically ill, wasted man. The thoracic findings were unimportant. Except for the terminal event of faintness, apprehensiveness and marked dyspnea, the symptoms were generally referable to the gastro-intestinal tract. At necropsy, a scirrhous adenocarcinoma of the stomach with pulmonary metastases was found. Besides the presence of lymphangitis carcinomatosa, an active thrombo-endarteritic process was strikingly conspicuous throughout the parenchyma of the lung.

Case 4.—H. W., a white man, aged 37, was admitted to the surgical service of Dr. Edwin Beer on July 16, 1931. The past history was unimportant except for an operation for perirectal abscess seven years previously. The patient stated that he had been in a good state of health until four months prior to his admission. About this time he became markedly constipated, and anorexia developed. Several days before his entrance to the hospital, severe diffuse pain developed in the upper abdominal region accompanied by several attacks of vomiting. Concomitant with the onset of the constipation he noted that he was short of breath after slight exertion and subsequently even while at rest.

Physical Examination.—The patient was an emaciated dyspneic man who appeared quite ill. Respirations were rapid (30 per minute) and "grunty." The pulse rate was 144, and the temperature 103 F. There were coarse loud râles and squeaks heard over both sides of the chest. The heart rate was rapid; no enlargement or murmurs were noted. The lower portion of the abdomen was distended, tense and tender from the umbilicus down to the symphysis pubis. No masses were palpated. Digital rectal examination revealed a hard, almost stony mass which encircled the rectum, slightly narrowing the lumen, just at the tip of the examining finger.

Laboratory Examination.—Examination of the blood showed a hemoglobin of 80 per cent, 6,000 white blood cells with 77 per cent polymorphonuclear leukocytes and 23 per cent lymphocytes. The urine contained albumin (2 +) and an occasional leukocyte. The stools were not examined. Because of the striking symptom of dyspnea, a roentgen examination of the chest was made soon after admission and

was reported by Dr. Harry Wessler as suggesting "lymphangitis carcinomatosa involving both lungs in their entirety."

Diagnosis.—The diagnosis was carcinoma of the rectum with peritoneal and pulmonary metastases and peritonitis secondary to perforation of a carcinomatous lesion.

Course.—While in the ward the patient's temperature varied between 103 and 104 F. with corresponding increase in the pulse rate varying between 100 and 136. The respiratory rate averaged about 31 per minute. The patient vomited frequently and complained of epigastric pain. There was diffuse abdominal tenderness. Dyspnea became more marked, and six days after admission he suddenly experienced cardiac collapse; the pulse became very rapid and thready; breathing was labored, accompanied by a marked diaphoresis. Death occurred one hour later on July 22, six days after admission to the hospital.

Autopsy.—Both pleural cavities were free from adhesions and did not contain any excess fluid. The lungs were well aerated and retained their shape. The visceral pleura presented numerous circular, umbilicated, firm nodules about 1 cm. in diameter scattered over the surface of the lung. Some of these nodules were confluent and were arranged in clover-leaf fashion. The appearance of white, firm cords of tissue in the lymphatics, spreading out from these nodules, was striking. On section, many similar grayish-white nodules were seen scattered diffusely throughout the substance of the lung, appearing to occupy particularly the septums and the peribronchial and perivascular areas. The nodules were larger and more confluent near the hilus, decreasing in frequency toward the periphery of the lung. The nodular involvement was greatest in the lower lobes. The hilus and paratracheal nodes were greatly enlarged and on section presented a grayish-white homogeneous structure. The lungs weighed 1,850 Gm. The pulmonary vessels were grossly normal.

The heart weighed 280 Gm. There was no hypertrophy of the right ventricle. The valves, endocardium and myocardium were grossly normal.

The liver weighed 1,675 Gm. The surface was smooth, and the capsule was not thickened. It was firm in consistency and reddish brown. The edges were rounded. On section, the lobular structure was distinct, the centers of the lobules being reddish brown. There were two grayish-white, round tumor nodules in the hepatic substances, measuring 3 mm. in diameter. The gallbladder, biliary passages and portal vein were normal. The lymph nodes in the porta hepatis were slightly enlarged.

The esophagus and stomach were essentially normal. The intestines were distended, being free in the upper part of the abdomen but densely matted in the lower half at the site of a peritoneal abscess formed after the rupture of a carcinoma of the sigmoid. The serosa, mesentery, mesocolon, mesosigmoid, omentum and parietal peritoneum all showed distinct, whitish-gray, firm, metastatic nodules, varying from 1 to 5 mm. in size. A distinctive feature was that the nodules were arranged in a linear or lacework manner as if they corresponded to the local lymphatic channels. At the junction between the descending colon and the sigmoid, the intestinal wall was thickened and infiltrated by firm, white tissue which continued for a distance of 15 cm., the sigmoid finally narrowing to a diameter of about 1 cm., causing marked stenosis of the lumen. The mucosal surface in this area was a dark dirty gray but not ulcerated. Just proximal to the stenotic lumen, a fistulous tract communicated with a peritoneal abscess which contained foul pus, sharply walled off by loops of small intestine and omentum. The remainder of

the sigmoidal and rectal mucosa was not involved. In the pelvic cavity the bladder, intestines and peritoneum were densely infiltrated with tumor tissue.

There were marked metastases with enlargement of many of the lymph nodes in the abdominal and thoracic regions. The thoracic duct could not be identified because of permission for a limited postmortem examination.

Microscopic Examination: The tumor in the sigmoid was described as an adenocarcinoma of the "signet ring" variety.

All the metastases examined histologically revealed the type of tissue seen in the primary neoplasm of the sigmoid.

This case showed strikingly a pure lymphangitic carcinomatosis. The most marked histopathologic changes were found in the perivascular and peribronchial lymphatics which were greatly dilated owing to the pressure of huge nests of tumor cells composed mostly of the signet ring type. Many of these collections of cells showed abundant secretion. Occasionally a mitotic figure was seen. The tumor caused a distinct narrowing and distortion of both the bronchi and bronchioles and the medium-sized and small arteries. The alveoli were similarly compressed, and the capillaries of their septums were congested. It is noteworthy that no appreciable amount of intimal hyperplasia was encountered.

Anatomic Diagnosis.—The diagnosis was adenocarcinoma of the sigmoid (signet ring cell type); lymphatic carcinomatosis of the peritoneum, mesentery, mesosigmoid, retro-aortic and retromediastinal nodes, bladder and intestines; lymphangitis carcinomatosa of the lungs; subacute infectious splenic swelling; metastatic nodules in the liver (minimal), and carcinomatous infiltration of the left ureter with left hydronephrosis.

Summary.—A 37 year old white man presented a history of constipation, anorexia and progressively increasing dyspnea for four months. Several days before entrance to the hospital severe pain in the upper abdominal region developed. Examination revealed an emaciated dyspneic man. The respiratory rate was 34 per minute. There were definite coarse râles in both sides of the chest. A stony hard mass was felt in the rectal wall. The presence of tachypnea with coarse râles in both sides of the chest in a case of neoplasm of the sigmoid led to the suspicion of pulmonary metastases—a suspicion which was confirmed by roentgen examination of the chest and autopsy.

At necropsy, an adenocarcinoma of the rectum was found with widespread lymphangitic metastases to the lungs without any histologic evidence of intravascular changes in the pulmonary vessels.

COMMENT

Pathology.—Of the four cases of carcinomatous lymphangitis of the lungs, only one (case 4) conforms with the picture of pure lymphatic dissemination stressed by the French authors. In this case the mediastinal lymph nodes were greatly enlarged by metastases from a carcinoma of the sigmoid. There was a diffuse involvement of the lymphatic vessels of the lungs which greatly compressed not only the alveoli but also the bronchioles, the medium-sized and smaller arteries and the arterioles. No endarteritic changes were noted in any of the vessels in this case.

In three of the four cases the presence of tumor cells in the perivascular lymphatics had called forth a marked increase in adventitial connective tissue as well as an intimal hyperplasia in many of the smaller

arteries and arterioles. Varying degrees of arterial obliteration were produced, often with complete closure of the lumen. This was especially conspicuous as widespread lesions in cases 1 and 2, and less widespread lesions in case 3.

It is perhaps more than a coincidence that the primary neoplasm in these three cases with vascular changes was a scirrhous carcinoma of the stomach. In some of the smaller arteries the intimal response might be ascribed to the invasion of the adventitia and a partial destruction of the media by scirrhous carcinoma. In other arterioles and small arteries, even after serial sections had been made, no such invasion was found. It is suggested that the presence of the carcinoma cells in the surrounding tissue exerted some stimulus which resulted in intimal hyperplasia and narrowing or occlusion of the vessels. This was suggested by the observation of a more or less marked inflammatory reaction around and in the outer wall of the vessels.

In routine microscopic examination of lungs showing lymphatic metastases from carcinomas of other abdominal organs, we have noted focal endarteritic changes in several instances, the affected vessels being surrounded by lymphatic vessels containing carcinoma cells.

An additional cause for the narrowing of the pulmonary arterial bed was seen in the apposition of a platelet thrombus on the hyperplastic intima. This thrombo-endarteritic process eventually resulted in either partial or total obliteration of the vessel. Often an eccentric lumen or one or more recanalizations were encountered (fig. 1).

Occasionally an embolus of carcinoma cells was found within a small artery or an arteriole in which varying degrees of obliterative endarteritis was present (fig. 3). This phenomenon was most marked in case 3. However, in all three cases the obliterating endarteritis was mainly the result of the perivascular carcinomatous lymphangitis and not, as M. B. Schmidt believed, principally the result of multiple carcinomatous emboli within the pulmonary arteries.

In sharp contrast to the fate of the carcinoma emboli in the arterioles and smaller arteries surrounded by lymphatic carcinosis is the end-result of carcinomatous emboli within the larger pulmonary arteries. In the larger pulmonary arteries a carcinoma embolus undergoes organization without inducing appreciable intimal damage and eventually becomes covered by endothelium. Such a sequence of events was recently observed in a case in which a primary carcinoma of the liver grew into the hepatic veins and resulted in the discharge of carcinoma cell emboli into the larger and medium-sized arteries. Microscopically, the deposition of the carcinoma emboli seemed to have caused no intimal damage in the vessels containing the emboli. The surface of the embolus (fig. 4) was lined by endothelium

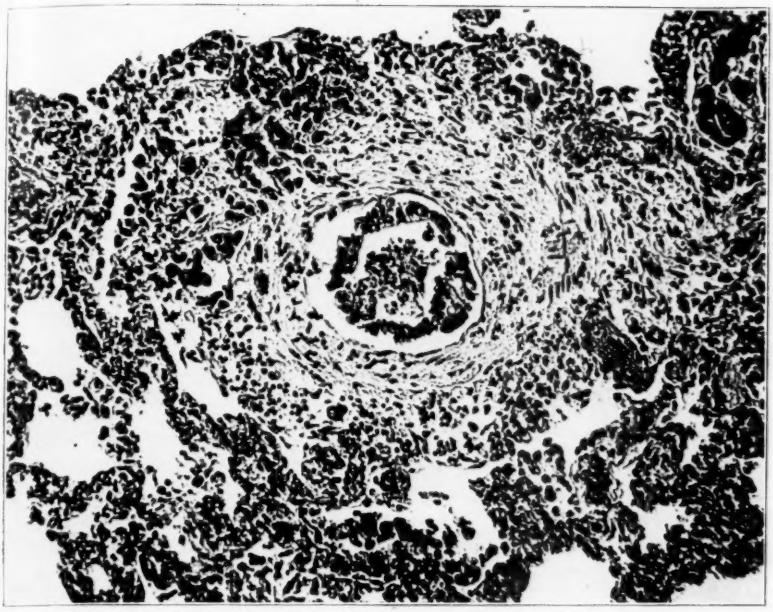

Fig. 3.—Small pulmonary artery showing carcinoma cells in perivascular lymphatics; perivascular fibrosis with narrowing of the lumen. Carcinoma cells are present within the lumen of the vessel.

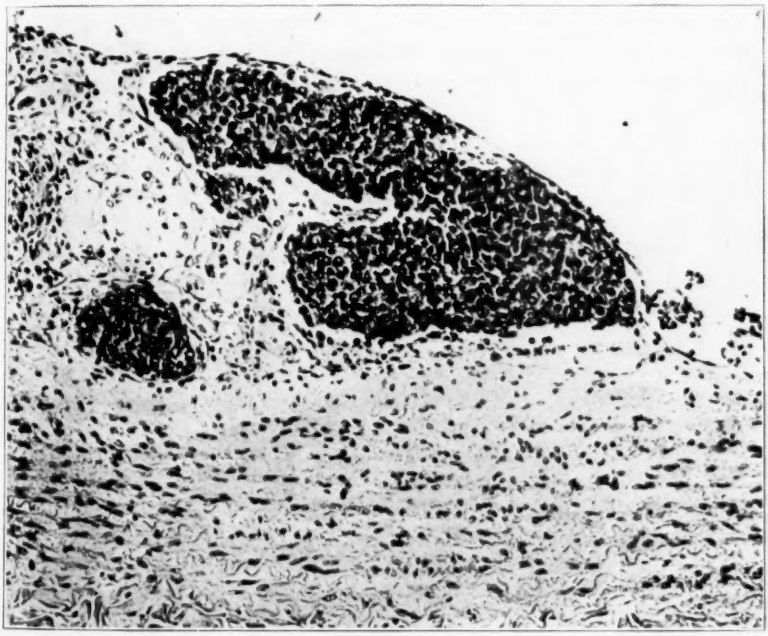

Fig. 4.—Carcinoma cell embolus lined by endothelium undergoing organization; the remainder of the arterial wall shows no changes.

and presented the usual changes characteristic of an ordinary pulmonary embolus undergoing organization. Another case serves to emphasize the difference between the end-results of emboli in larger arteries and in arterioles. In this case focal carcinoma cell emboli in the pulmonary arteries resulted from involvement of the hepatic veins by a carcinoma of the gallbladder. The intima of the large arteries which contained emboli showed no change although the perivascular lymphatics of the vessels contained tumor cells. In arterioles which contained carcinoma emboli and which were surrounded by lymphatic metastases, a typical obliterative endarteritis was regularly present.

Clinical Characteristics.—Cases 1 and 2 presented a striking picture of progressive dyspnea, cyanosis and finally right ventricular cardiac failure. In the second case the increasing tachypnea, the deepening cyanosis with progressive enlargement of the liver and the generalized edema in the absence of diagnostic pulmonary or cardiac findings made the diagnosis difficult.

Case 3 revealed no clinical features indicative of the underlying pulmonary disease. In this case the increasing constipation with progressive loss of weight and weakness dominated the clinical picture.

In case 4 the presence of tachypnea with disparagingly few pulmonary signs and the presence of a carcinoma of the sigmoid prompted the diagnosis of carcinomatous lymphangitis secondary to a colonic neoplasm. In this case dyspnea was probably the direct result of the mechanical compression which not only diminished the available alveolar respiratory area but also narrowed the pulmonary circulation, thereby embarrassing the oxygen supply of the patient.

It is diagnostically important to bear in mind that when a clinical picture is presented of right ventricular failure without obvious cause and without any conspicuously abnormal physical signs in the lungs, the suspicion of carcinomatous lymphangitis of the lungs should be entertained, a fact that was pointed out by Troisier. Since neoplasms of any of the abdominal organs may give rise to pulmonary metastases, it is reasonable to expect that they may cause right ventricular failure. Excluding primary carcinoma of the bronchus, which usually gives conspicuous signs and symptoms in the respiratory tract, carcinoma of the stomach is (in our experience) the most frequent cause of carcinomatous lymphangitis of the lungs and arteriolar occlusions.

Dyspnea and cyanosis are the two most constant clinical features of failure of the right ventricle, and in the first two cases failure of the right side of the heart is clearly the result of the progressive obliteration of the pulmonary arterioles and the smaller arteries. Dunn [14] has pro-

14. Dunn, J. S.: The Effects of Multiple Embolism of Pulmonary Arterioles, Quart. J. Med. **13**:129 (Jan.) 1920.

duced multiple embolisms of the pulmonary arterioles experimentally by intravenous injection of granules of starch. He found that with a degree of embolism insufficient to produce death there was a great increase in the frequency and a diminution in the depth of respiration (rapid shallow breathing).

The interpretation of the clinical findings is greatly aided by roentgen examination of the lungs. In cases 1 and 4 the presence of numerous streaks radiating from an enlarged hilar shadow made the pulmonary fields appear mottled and suggested the diagnosis of carcinomatous lymphangitis. Assmann [15] and Wessler [16] must be credited with having pointed out that this roentgenologic picture is suggestive of pulmonary carcinomatous lymphangitis.

SUMMARY

Four cases of carcinomatous lymphangitis are described.[17] Three were secondary to scirrhous adenocarcinoma of the stomach and one to adenocarcinoma of the sigmoid. In all four, the physical signs of the pulmonary involvement were inconspicuous and yet the clinical picture was characterized by an initial cough and by rapidly increasing dyspnea and deepening cyanosis. Two of the four patients died with evidences of rapidly progressive failure of the right side of the heart. The roentgen diagnosis of carcinomatous lymphangitis of the lungs was confirmed by necropsy in two cases. In the three cases of scirrhous adenocarcinoma of the stomach, autopsy revealed a widespread obliterative endarteritis of the smaller pulmonary vessels. In two of these cases the vascular changes were sufficiently extensive to explain the failure of the right side of the heart.

This obliterative endarteritis is due mainly to the influence of the plugging of the neighboring perivascular lymphatic channels by carcinoma, so-called carcinomatous lymphangitis. The vascular occlusions result to a minor degree from carcinoma cell emboli which have entered the pulmonary circulation via the thoracic duct and the superior vena cava. A few carcinoma cell emboli were found which had accumulated blood platelet thrombi in their passage through the blood stream and subsequently had undergone rapid organization after they had come to lodge in small branches of the pulmonary arteries.

15. Assmann, H.: Klinische Roentgendiagnostik der inneren Erkrankungen, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 314.

16. Wessler, H.: Personal communication.

17. Since this presentation was made before the Pathological Society in May 1933 two other similar cases have been observed; one was observed through the courtesy of Dr. W. Antopol, pathologist to the Bayonne Hospital, Bayonne, N. J.

CONCLUSIONS

1. Four cases of carcinomatous lymphangitis of the lung are reported, three secondary to scirrhous carcinoma of the stomach and one secondary to an adenocarcinoma of the sigmoid.

2. The four cases presented all or part of the pulmonary symptoms of cough, tachypnea and cyanosis with inconspicuous physical signs in the lungs.

3. The three cases secondary to scirrhous carcinoma of the stomach presented diffuse obliterative endarteritis of many pulmonary arterioles and small arteries.

4. The widespread obliterative endarteritis of the lung was due chiefly to the influence of the carcinomatous lymphangitis of the neighboring perivascular lymphatics, rarely to carcinoma cell emboli.

5. In two of the cases right ventricular cardiac failure was the direct result of the diffuse obliterative endarteritis of the pulmonary vessels.

6. In cases of right ventricular cardiac failure presenting no significant pulmonary or cardiac findings, the possibility of a diffuse secondary carcinomatous lymphangitis of the lungs with accompanying obliterative endarteritis of the pulmonary vessels should be considered.

ACUTE ESSENTIAL HYPERTENSION PRECIPITATED BY MEDIASTINAL ABSCESS

C. A. McKINLAY, M.D.

THOMAS J. KINSELLA, M.D.
AND
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MINNEAPOLIS

While mediastinal abscess following trauma probably occurs infrequently enough to justify an individual report, the case under consideration challenges particular attention because of an associated acute arterial hypertension. Not only did hypertension of pronounced intensity of both systolic and diastolic phases develop directly and coincidentally with the process, but there was a gradual fall to normal limits as healing occurred. No similar instance was found in a rather extensive search through the medical literature. The implications as to the theory of the etiology of essential or nonrenal hypertension stimulate the imagination, although admittedly an acceptable rationalization may elude us at this time.

REPORT OF A CASE

History.—A man, single, aged 21, a student and a member of the football squad, was admitted to the University Hospital on Friday, Sept. 23, 1932, with a complaint of pain in the chest, a chilly sensation and fever. The pain followed an injury sustained in football practice two days previously. The patient did not know or remember the incident of the injury, simply that at some time in the afternoon while in scrimmage his chest had been hurt. There had been no extreme pain, and he had indulged in three or four other scrimmages before being admitted to the hospital. The patient had been feverish since the injury, with chilly sensations during the second night.

His past history and that of his family were unimportant. A complete routine physical examination before the present illness revealed a displaced nasal septum due to a football injury, slight dental caries, tonsillar tags, varicocele on the left side and hemorrhoids. Urinalysis showed no albumin or sugar. The reaction to the Mantoux test was negative. The blood pressure five days before injury was 124 systolic and 86 mm. of mercury diastolic. Examination one year previously had shown a blood pressure of 128 systolic and 84 mm. of mercury diastolic.

Examination.—On entrance, the temperature was 103 F., the pulse rate, 104, and the respiratory rate, 28. The pharynx was injected. There was tenderness over the entire sternum. No abnormal physical signs in the chest were noted; the breathing, however, was restricted bilaterally. Roentgenograms showed

From the Students' Health Service and the Department of Surgery, University of Minnesota.

a linear fracture of the sternum without displacement 3 cm. below the manubriosternal juncture. The lungs were normal.

Course.—On the fourth day of continued high temperature, increased cough and sputum were noted. On the sixth day, slight cyanosis, an increased respiratory rate, fever and blood-tinged sputum, together with dulness and suppression of breath sounds and increased tactile fremitus above the right base posteriorly indicated pneumonia. There was moderate edema above the sternum. A roentgenogram showed infiltration above the right side of the diaphragm suggestive of a bronchopneumonia. The leukocyte count had increased from 8,000 to 13,500. Pneumococcus type A was recovered from the sputum. On the seventh day, increased swelling over the sternum was noted. On the ninth day, the temperature was lower and the general condition was satisfactory. On the tenth day, however, the patient appeared to be more prostrated and was extremely ill with

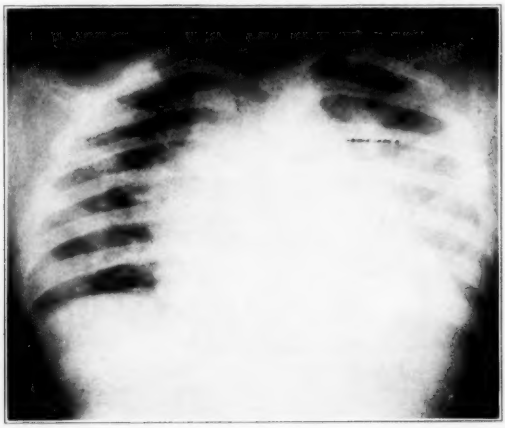

Fig. 1.—Roentgenogram of chest on tenth day of illness. This shows especially the widening of the mediastinum.

marked edema of the entire upper part of the anterior chest wall. The posterior part of the left pulmonary field showed impairment of resonance and diminished breath sounds. The heart tones were somewhat diminished. A pleuropericardial friction rub was heard along the left cardiac border, but no to and fro friction was noted. It was recognized that bronchopneumonia alone could not account for the clinical picture. Emphasis was placed on the significance of the edema of the sternum and upper part of the anterior thoracic wall, and mediastinitis was recorded as a probable diagnostic consideration. A roentgenogram taken on the tenth day of the illness (fig. 1) revealed a decided change, interpreted as probably bronchopneumonia with possible fluid on the left side and marked widening of the mediastinum. The leukocyte count had increased to 21,800. A second blood culture was reported negative. On the eleventh day, there was continued marked prostration with increased cyanosis. Continued emphasis was placed on the edema of the upper part of the anterior thoracic wall which was considered to be of intrathoracic origin. The point of maximum cardiac impulse was forceful and

was noted 4 cm. beyond the nipple line. No pericardial or pleural friction rub was heard. The systolic blood pressure was 142 mm.; the diastolic pressure was not recorded.

On the twelfth day, the patient was more prostrated; the pulse rate had increased to 120, but the temperature was reduced to 99.8 F. This remarkable spread in the temperature and pulse (fig. 2) was coincidental with a decided increase in the systolic blood pressure to 194, indicating that a definite change in the control of the vasomotor function had occurred. The respiratory rate remained elevated between 36 and 40 when the patient was in an oxygen tent.

A remarkable physical finding which had appeared overnight, noted by one of us (C. A. McK.), was the presence of a fluctuating mass about 5 cm. in diameter situated above and to the left of the midsternum. This mass definitely varied in size with respiration, increasing with expiration and decreasing with inspiration, showing its intrathoracic origin. The cardiac impulse was transmitted through the mass, although there was no expansile pulsation. The edema of the surrounding tissues had not increased.

A roentgenogram taken immediately after the discovery of the fluctuating mass was interpreted as showing extensive pneumonia or pleural effusion on the right side, resolving pneumonia on the left side and distinct narrowing of the mediastinal shadow as compared to the examination two days previously. This film does not lend itself satisfactorily for purposes of publication.

It now seems probable that the narrowing of the mediastinal shadow was due to the rupture of the mediastinal abscess into the anterior part of the thoracic wall and also into the right pleural cavity. The latter event is only conjecture, although injection of an opaque medium later showed a connection between the mediastinum and an anterior empyema pocket.

A diagnosis of abscess of the anterior mediastinum pointing through the sternum was made, with which Dr. S. Marx White and Dr. T. J. Kinsella, as consultants, concurred. Within five hours after its appearance and recognition, the abscess was drained through a left upper parasternal incision by one of us (T. J. K.), and 400 cc. of thin purulent material was obtained. The pus escaped from the mediastinum through the fractured sternum, the edges of which were separated about 5 mm., and through a defect produced by the traumatic separation of the left third costal cartilage from the sternum. No accessory pockets were found in the mediastinum, but a left subpectoral pocket was opened and drained. Culture from the pus revealed both streptococci and staphylococci. An airtight dressing sealed with strips of adhesive tape was applied to prevent respiratory embarrassment from the sucking mediastinal wound. This was later replaced by a metal cage moulded to the contour of the thoracic wall and sealed to the skin, in which a constant negative pressure of from 10 to 15 cm. of water was maintained by means of a suction pump. A removable cap permitted change of dressing without disturbing the skin seal.

A blood culture taken the day following drainage was positive for staphylococci. The leukocyte count had increased to 30,000. Roentgenograms showed a homogeneous density on the right and numerous areas of density on the left, and suggested an extensive pneumonia. On the second day following drainage, or the fourteenth day of the illness, the blood culture showed staphylococci on both broth and plate, and the wound smear and sputum showed a pure culture of the same organisms. Blood cultures on the fifteenth and sixteenth days showed fewer colonies, not more than six on a plate, and on the seventeenth and eighteenth days, no growth. On the twentieth day, the leukocyte count had fallen to 21,800, and on the twenty-seventh day, to 9,850.

Following development and drainage of the abscess, the temperature remained lower, but the pulse rate was accelerated, and the rate of respiration increased. Dyspnea was pronounced. Cyanosis was moderate, and the patient's comfort was enhanced by the oxygen tent. The blood pressure remained elevated. On the fifteenth day, another wave of increased temperature occurred. On the sixteenth day, however, the pulse rate was slower and there was definite improvement in the patient's general condition, with less labored breathing. There were no petechiae noted in the skin. On the seventeenth day, a small vesicular rash appeared at points of irritation on the skin, described as miliaria by a dermatologist; the leukocyte count reached 37,000. MacNeal bacteriophage (asparagine medium) was given intravenously at the suggestion of Dr. Diehl, director of the Students' Health Service, after his careful study of its specificity for the organism involved. Bacteriophage (veal broth mediums prepared by Dr. W. P. Larson) was dropped into the mediastinal wound four times daily. On the nineteenth day, general improvement was noted. Because of suggested signs of fluid at the base of the right lung, aspiration was attempted on the twentieth day, but no fluid was found. The temperature assumed a lower level (maximum, below 100 F.), and the general condition remained satisfactory. On the twenty-first day, a roentgenogram showed considerable clearing of the shadows on both the right and the left side. By the twenty-seventh day a roentgenogram showed evidence of pleural effusion on the right side, although there was no change in the patient's general condition. On October 18, thoracentesis was performed and 60 cc. of thin pus was obtained posteriorly from the right pleural cavity. The temperature at this time varied from normal to 99.6 F., and the pulse rate from 90 to 100. There were no chills. Roentgenograms after injection of an iopax derivative into the mediastinal wound showed a connection between this area and an anterior empyema pocket which may have allowed drainage of the empyema and accounted for its relatively benign character.

Aspiration of the empyema cavity was performed at intervals of from three or four days, and asparagine medium bacteriophage was injected at the times of aspiration. Streptococci and staphylococci were cultured in the empyema fluid. On November 1, a closed catheter drainage was done under ethylene anesthesia. At this time, the mediastinal wound was practically closed, although light drainage was still present. Crepitus was still present at the site of the fracture and a roentgenogram of the site of the fracture showed considerable destruction with, however, some new bone formation.

The empyema cavity was irrigated with a surgical solution of chlorinated soda thereafter at two hour intervals. The general condition was good; the temperature was 99.6 F., the pulse rate, from 100 to 110, and the respiratory rate, 24. On Dec. 5, 1932, the patient was discharged from the hospital with the drainage tube in place. Irrigation with solution of chlorinated soda was continued. On Feb. 11, 1933, the tube was removed after repeated cultures of the serous material obtained had shown no growth and the cavity held less than one ounce of it. The mediastinal wound was entirely healed. The blood pressure on numerous occasions was never more than 126 mm. systolic. Figure 2 shows a composite record for the first part of the illness.

The empyema cavity refilled, however, and after several aspirations a subperiosteal resection of portions of the eighth and ninth ribs on the right side was done March 15, 1933, under local infiltration with 1 per cent procaine and epinephrine, and ethylene anesthesia. The blood pressure, which at the onset of the operation was 130 systolic and 70 diastolic, rose ten minutes later to 200 systolic and 90 diastolic, and fluctuated from 160 systolic and 80 diastolic to 170 systolic

and 60 diastolic at the close of the operation. The subsequent course was quite satisfactory. Irrigation with the solution of chlorinated soda was continued, and the cavity gradually decreased in size, as shown by injections of iodized oil, until it was entirely obliterated. The tube was removed Sept. 1, 1933. The mediastinal wound was likewise well healed, and a roentgenogram of the fracture showed firm union, with good callus. There had been considerable loss of weight, and muscular atrophy was quite evident, especially on the right side of the chest. With the resumption of the patient's normal activities, including football and basketball, there was return to normal of both body weight and muscular development.

The eyegrounds were considered normal on several examinations. The blood pressure in the lower extremities approximated that in the upper. Pressure over the sinus caroticus caused no appreciable alteration in the pulse rate.

Special atttention was paid to renal function on account of hypertension, but at no time was there any evidence of nephritis. The urine was free from albumin

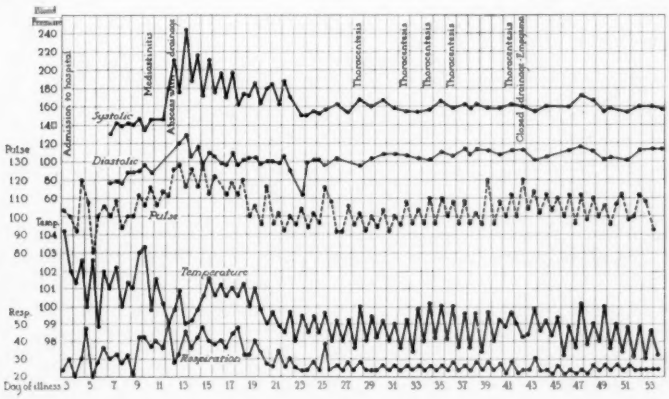

Fig. 2.—Composite chart of temperature, pulse rate, respiratory rate and blood pressure. Blood pressure had returned to normal on the seventy-fifth day of illness.

on seven of eight examinations, and at the time of the one exception, which occurred at the height of the fever and the pneumonic process, it contained only a light cloud. The specific gravity ranged from 1.017 to 1.030, and the sediment was entirely free from red blood cells and casts. The phenolsulphonphthalein test on the twenty-seventh day showed elimination of 68 per cent in two hours. The blood urea nitrogen on the thirteenth day, at the height of the pneumonic process, was 50 mg., but four days later it was checked at 28.9.

The possibility that this case might represent a potential case of hypertension or a prehypertensive stage was considered. In accordance with the recent work of Hines and Brown,[1] the vasomotor reaction after immersion of the hand in ice-water was obtained. Readings well within the normal response were found.

1. Hines, E. A., Jr., and Brown, G. E.: Standard Test for Measuring Variability of Blood Pressure; Its Significance as Index of Prehypertensive State, Ann. Int. Med. **7**:209 (Aug.) 1933.

The familial aspect of hypertension was investigated. The father and mother were each in good health. The blood pressure of the father (aged 53) was 160 systolic and 100 diastolic; the mother (aged 46) gave readings of 134 systolic and 80 diastolic.

COMMENT

Mediastinal abscess itself is rare. While it is not within the scope of this article to attempt a complete survey of reports of its occurrence, it may be mentioned that as long ago as Galen's time, mediastinal abscess was recognized, and this author recorded a case following trauma. Hare [2] collected a series of 115 cases of mediastinal abscess. Dunham [3] noted in the army records of 3,889 nontraumatic cases of empyema, 67 instances of acute mediastinal infection in 531 necropsies. It may be noted that simple nonsuppurative mediastinitis is usually a complication of some nearby inflammatory disease, such as pericarditis, pleurisy or pneumonia. Gaarde [4] called attention to the frequency with which suppurative mediastinitis or empyema was found post mortem in pneumonia complicating the influenza epidemic of 1918 and 1919. The chief diagnostic sign that he noted was substernal pain. He noted also that abscess was much less likely to give pressure symptoms than a solid tumor. Other causes noted by him were: (1) trauma, especially puncture wounds, perforation of the esophagus due to ulceration caused by a malignant condition, corrosive poisoning or instrumentation and descending infections of the neck, such as Ludwig's angina or retropharyngeal abscess; (2) direct extension of Pott' disease, and also extension secondary to tuberculosis of the rib or cartilage. Graham [5] mentioned as a cause rupture of the mediastinal glands and, rarely, empyema. He mentioned edema of the upper part of the chest and swollen veins as important diagnostic signs; likewise, that involvement of the vagus may cause disturbance of the cardiac rhythm, gastric symptoms and vomiting. Graham also considered that the diagnosis of acute mediastinitis is often extremely difficult and can be made only when abscess is present; and that acute inflammation of the mediastinum should always be regarded as a very serious condition with a grave prognosis. Blankenhorn [6] stated that acute infectious processes of the mediastinum are usually traumatic and,

2. Hare, H. A.: The Pathology, Clinical History and Diagnosis of Affections of the Mediastinum Other Than Those of the Heart and Aorta, Philadelphia, P. Blakiston's Son & Co., 1889.

3. Dunham, E. K.: Infection in Mediastinum in Fulminating Empyema, Surg., Gynec. & Obst. **35**:288 (Sept.) 1922.

4. Gaarde, F. W., in Blumer, George: Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, vol. 2, p. 263.

5. Graham, E. A.: Surgical Diagnosis, Philadelphia, W. B. Saunders Company, 1930, vol. 3, p. 163.

6. Blankenhorn, M. A., in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1931, vol. 3, p. 571.

if not promptly fatal, lead to formation of abscesses. The medical aspects of acute mediastinitis are seen in the profound disturbance of the pulse rate, and occasionally of respiration, as a result of vagus and phrenic neuritis.

McLester [7] stated that mediastinitis occurs, in order of frequency, by extension, metastasis or trauma, and that it occasionally occurs after fracture of the sternum. The prognosis is grave but not hopeless, depending on prompt recognition and surgical intervention. In this connection, Woodroffe [8] reported 2 cases of traumatic mediastinal abscess in soldiers, with recovery. He was unable to find a report of a single case in the British army during war.

Laryngeal symptoms from pressure on the vagus and recurrent nerves are referred to occasionally as dominating the picture in mediastinitis. In 1875, Johnson [9] stated that either bilateral spasm or palsy of the larynx may follow. Lemon [10] reported 23 cases with lesions affecting the vagus nerve from the jugular foramen to the arch of the aorta chiefly, with symptoms from involvement of the recurrent laryngeal nerve. Together with Doyle,[11] he noted that in 26 cases of Hodgkin's disease with mediastinal involvement, the recurrent laryngeal, vagus and sympathetic nerves escaped direct pressure. No changes in blood pressure were recorded. Gaarde,[12] at the Mayo Clinic, kindly reviewed the blood pressure readings in 64 cases of mediastinal affections, chiefly tumor. Only 2 cases of mediastinal abscess were observed, both with normal readings. Mediastinitis in 11 other cases was associated once with hypertension. Gaarde is under the impression that the total incidence of hypertension in the whole group was no greater than might be expected in any similar age group.

In the absence of special notations as to blood pressure in mediastinal conditions in the available descriptions, it was of interest to note that Villaret [13] and his co-workers, in 1926, reported in a case of lymphosar-

7. McLester, J. S., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1932, vol. 2, p. 197.

8. Woodroffe, H. L. W.: Mediastinal Abscess, Dublin J. M. Sc. **146**:1 (July) 1918.

9. Johnson, George: On the Laryngeal Symptoms Which Result from the Pressure of Aneurismal and Other Tumours on the Vagus and Recurrent Nerves, Med.-Chir. Tr., London **58**:29, 1875.

10. Lemon, W. S.: Lesions Affecting Vagus Nerve, M. Clin. North America **7**:293 (July) 1923.

11. Lemon, W. S., and Doyle, J. B.: Clinical Observations of Hodgkin's Disease, with Special Reference to Mediastinal Involvement, Am. J. M. Sc. **162**: 516 (Oct.) 1921.

12. Gaarde, F. W.: Personal communication to the authors.

13. Villaret, M., and others: Paroxysmal Attacks of Hypertension in Course of a Lymphosarcoma of Superior Mediastinum, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1215 (July 9) 1926.

coma of the superior mediastinum, paroxysmal hypertensive crises and also paroxysmal dyspnea. The main feature in this fatal case of lymphosarcoma in a woman, aged 75, was the occurrence of paroxysmal hypertensive attacks synchronous with severe crises of dyspnea with stridor of from one-half to one hour's duration. Necropsy revealed lymphosarcoma in the superior mediastinum involving the right vagus nerve with pressure in three areas, as shown by careful dissection. The authors considered that vagotonia existed because of slowing of the pulse rate from 110 to 60, and because atropine reduced the dyspnea without much influence on the blood pressure. They considered as incontestable the existence of the transitory hypertensive attacks through mediastinal irritation of the vagus. They noted no similar reference except that of Harvier and Bariéty,[14] who reported in a case of carcinoma of the esophagus paroxysmal attacks of loud inspiratory dyspnea associated with arterial hypertension.

Speculation as to the physiologic factors should be briefly considered in view of the increased knowledge of the depressor or aortic nerve, with its receptors in the aortic wall, which transmit impulses that reflexly regulate blood pressure, heart rate and suprarenal secretion. Hering[15] showed that in the rabbit the depressor nerve runs separately, and its excision is followed by a persistent elevation of blood pressure. Starling[16] stated that the depressor nerve in the rabbit is vagus in origin, one root arising from the trunk of the vagus and the other from the superior laryngeal branch of the vagus. In the dog, the depressor nerve runs in the vagus trunk, together with the sympathetic nerve, for the greater part of its course. The sinus nerves, likewise, according to Hering[15] and Koch,[17] exhibit a tonic inhibitory influence on the circulation. Section of the nerves causes pressor effects. Duncan,[18] after anatomic study in man, pointed out that a nerve resembling the isolated depressor in the rabbit is rarely found. Braeucker[19] concluded from his own work and from that of Jonnesco and Ionescu[20] that depressor

14. Harvier, P., and Bariéty, M.: Laryngeal Crises with Cancer of Esophagus, Bull. et mém. Soc. méd. d. hóp. de Paris **49**:176 (Feb. 6) 1925.

15. Hering, H. E.: Die klinische Bedeutung der Carotissinusreflexe, Klin. Wchnschr. **6**:232 (Jan. 29) 1927.

16. Starling, E. H.: Principles of Human Physiology, edited and revised by C. L. Evans and H. Hartridge, ed. 5, Philadelphia, Lea & Febiger, 1930.

17. Koch, E.: Die reflektorische Selbsteuerung des Kreislaufes, in Kisch, Bruno: Ergebnisse der Kreislaufforschung, Dresden, Theodore Steinkopff, 1931, vol. 1.

18. Duncan, D.: Anatomy of Depressor Nerve in Man, Arch. Neurol. & Psychiat. **21**:1010 (May) 1929.

19. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinisch chirurgische Bedeutung, Beitr. z. Klin. d. Tuberk. **66**:1, 1927.

20. Jonnesco, Theodore, and Ionescu, D.: Experimentelle Untersuchungen, Ztschr. f. d. ges. exper. Med. **48**:490, 1926.

fibers exist in man in two cardiac branches of the sympathetic system and in more than one cardiac branch of the vagus. S. Wright,[21] in a summary, stated that late evidence is against the emergency-epinephrine-secretion theory of Cannon,[22] and favored that of Tournade,[23] whose experiment consisted of drawing blood from the suprarenal vein of a normal animal into the jugular vein of an animal after suprarenalectomy. In the recipient, this caused the blood pressure to rise, the arteries to constrict and the rate of the heart to increase. Tournade et al [23] also showed that this mechanism assisted in steadily maintaining blood pressure, for if the blood pressure is lowered in the donor by hemorrhage, the secretion of epinephrine is increased. Heymans,[24] in 1929, found that the secretion of epinephrine is reflexly controlled by the aortic and the sinus nerves. Houssay and Molinelli,[25] 1924, showed that the vagus nerve also contains afferent fibers which can increase the secretion. Wright [21] stated that these experiments prove convincingly that secretion of epinephrine is reflexly adjusted by means of the aortic and sinus nerves, and that neither the glandular nor the bulbar centers are acted on directly by the level of the blood pressure. At rest, the aortic and sinus nerves seem to exert in the main a tonic inhibitory influence over the activity of the suprarenal glands. Nathanson's [26] observation that minute doses of epinephrine administered subcutaneously release the heart from the depressor effect of the stimulation of the sinus caroticus should be mentioned.

In the rabbit, after excision of the depressor nerve with resultant persistent hypertension, certain pathologic changes, such as thinning of the media and thickening of the intima in the aorta by proliferation, and sclerosis of the pulmonary vessels have been described. Hering [15] pointed out that these arterial changes resemble those occurring after injection of epinephrine, and he was inclined to attribute them, and also the hypertension, in part, to the hyperadrenalinemia following division of the buffer nerves. Wright [21] raised the question as to what extent hypertension and arteriosclerosis in man may be attributed to the loss of afferent control of the bulbar centers.

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21. Wright, S.: Lecture on Recent Work on Afferent Control of Circulation in Health and Disease, Brit. M. J. **1**:457 (March 12) 1932.

22. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear, and Rage, New York, D. Appleton and Company, 1915.

23. Tournade, A., and Chabrol, M.: Proof of Reflex Secretion of Epinephrine, Compt. rend. Soc. de biol. **92**:418 (Feb. 20) 1925.

24. Heymans, C.: Le sinus carotidien isolé et pérfuse, zone réflexogène régulatrice de l'adrénalinosécrétion, Compt. rend. Soc. de biol. **100**:199 (Jan. 25) 1929.

25. Houssay, B. A., and Molinelli, E. A.: Reflex Secretion of Epinephrine, Compt. rend. Soc. de biol. **91**:1056 (Nov. 14) 1924.

26. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933.

While the connection is remote, the interesting cases of tumor of the suprarenal gland with hypertension should be mentioned. Fishberg and Oppenheimer,[27] in 1924, reviewed 15 reported cases of chronic nonnephritic hypertension associated with anatomically demonstrable lesions of the suprarenal glands. Rogers [28] reported a case of ganglioneuroma of the suprarenal medulla and postulated imbalance of the vegetative nervous system because of paroxysms of hypertension, disturbance of the carbohydrate metabolism in the absence of a pancreatic lesion, elevation of the basal metabolic rate and gastric disturbances. In addition, it is known that stimulation of the hypothalamus may produce a rise in the blood pressure and secretion of epinephrine. Penfield,[29] 1929, described a case of thalamic tumor involving the mesial nuclei in which there were attacks of hypertension.

Physiologically, asphyxia and an excess of carbon dioxide affects the vasomotor center, producing a rise in blood pressure. The asphyxia of carbon monoxide poisoning may produce a rise in blood pressure. Pain or any stimulation of a sensory nerve may cause an acute hypertension. However, the hypertension noted in this case persisted for a greater length of time than any of the possibilities just mentioned, even though they had been operative. Likewise, the cyanosis seen in uncomplicated cases of lobar pneumonia, which may be interpreted as meaning at least a degree of oxygen deficiency and excess of carbon dioxide, is seldom associated with hypertension. In this case, the blood pressure remained elevated after cyanosis had disappeared. Dr. E. T. Bell,[30] of the department of pathology of the University of Minnesota, suggested the possibility of involvement of a depressor nerve. Dr. F. H. Scott,[31] of the department of physiology at the University of Minnesota, considered that involvement of a depressor nerve was possible, but he was inclined to ascribe the effect to mechanical factors.

In view of these physiologic considerations, it appears that this case of hypertension, developing coincidentally with mediastinal abscess, has important implications. While the effect of the vagus in slowing the heart rate was not apparent, the development of hypertension with tachycardia exactly coincident with the development of mediastinitis and mediastinal abscess, and receding following surgical drainage as the process healed suggested, in the absence of renal or other causes, a pro-

27. Fishberg, A. M., and Oppenheimer, B. S.: Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

28. Rogers, E.: Paroxysmal Hypertension Associated with Ganglioneuroma of Suprarenal Medulla, Am. Heart J. **8**:269 (Dec.) 1932.

29. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

30. Bell, E. T.: Personal communication to the authors.

31. Scott, F. H.: Personal communication to the authors.

found change in the vasomotor regulatory mechanism. In view of the lesion which, according to Braeucker,[19] anatomically could have involved the course of the afferent aortic nerves, a rational explanation on consideration of physiologic and pathologic data may be postulated. These data consist of the established importance of the afferent buffer or depressor nerves which assist in maintaining normal blood pressure through tonic inhibitory influence on the bulbar centers through control, in part, of suprarenal secretion. Its proved involvement in one case [13] of neoplasm was associated with transient attacks of dyspnea and hypertension. In another case of carcinoma of the eosphagus, involvement of the recurrent nerves was associated with similar transient attacks of hypertension and dyspnea.

It appears, therefore, entirely possible that fibers of the afferent buffer mechanism were directly involved in the area of the suppurative mediastinitis. If new conceptions of the mode of action of the depressor nerves are considered, the physiologic mechanism includes the increase in secretion of epinephrine.

SUMMARY AND CONCLUSIONS

A case is reported in which, following fracture of the sternum, pneumonia, mediastinitis and mediastinal abscess developed and were recognized in sequence. Coincident with suppurative mediastinitis and pointing of abscess through the line of fracture to the subcutaneous tissues, an acute hypertension developed. This was not associated with renal or other previously recognized or recorded provocation. Simultaneous elevation of the pulse rate in the presence of lower temperature indicated a profound alteration in the vasomotor regulatory mechanism.

In view of the unique nature of this case, speculation as to the etiology was in order. On the basis of physiologic considerations and anatomic relations, the possibility is here suggested that the mediastinitis and abscess involved the depressor nerves, approximating the effect of a total resection with the resultant hypertension seen in experimental animals. Mechanical effects cannot be ruled out as a cause, although in the literature reviewed, mediastinal neoplasms causing decided pressure were not found to precipitate hypertension, except in one instance of neoplastic involvement of the right vagus nerve.

We believe that an additional precipitating cause of acute nonrenal hypertension has been recorded with the report of this case.

Students' Health Service.

News and Comment

CENTRAL SOCIETY FOR CLINICAL RESEARCH

The seventh annual meeting of the Central Society for Clinical Research will be held in the Tropical Room of the Medinah Club, 505 North Michigan Avenue, Chicago, on Friday, November 2, and Saturday morning, November 3.

The Central Society for Clinical Research was founded and organized largely through the initiative and energy of Dr. Frank Billings. It was his desire to establish a society which would be a common meeting place for the younger physicians in the cities and villages of the Middle West and which would serve to maintain their interest in scientific medicine and clinical research. He lived to see assured the success of the society in which he was so interested. The meetings are open to all.

Book Reviews

Obstetric Medicine. Edited by Fred L. Adair, M.D., Professor of Obstetrics and Gynecology, University of Chicago, and Edward J. Stieglitz, M.D., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago. Price, $8. Pp. 743, with illustrations. Philadelphia: Lea & Febiger, 1934.

As the editors state, this book is an effort to coordinate and correlate the medical knowledge concerning the problems of diagnosis, therapy and prognosis of disease occurring coincidentally with pregnancy. It is written by thirty-nine well known contributors under the editorship of two.

It is a fairly good textbook of medicine. To be sure, it treats of many conditions that appear to have little to do with ordinary pregnancy, for example, African sleeping sickness and Schistosoma japonicum "endemic in Japan, the valley of the Yangtse River in China, in the Philippine Islands, Singapore, and the Shan States." But the book in general is modeled on standard lines. The infectious diseases and the various systemic disorders, including diseases of the teeth, eyes and skin, are competently discussed. The blood and the endocrine glands receive adequate consideration, and there is an excellent chapter on deficiency disease as related to pregnancy, while allergy and industrial poisoning, as well as drug habits, receive an appropriate amount of attention. The commendable feature of the volume lies in the imagination behind it, for a reference book of this sort should be of great value; the disadvantage is that in its present form the book is neither a particularly first class textbook of obstetrics on the one hand, nor a particularly first class textbook of general medicine on the other, but a somewhat unconvincing mixture.

Die Tonuskrankheiten des Herzens und der Gefässe. By Professor J. Pal. Price, 18 marks. Pp. 228, with 20 illustrations. Vienna: Julius Springer, 1934.

This monograph deals with various problems concerned in the regulation of blood pressure. After an introductory chapter, hypertension is discussed at considerable length. The author recognizes two kinds of hypertension: transitory hypertension from vascular spasm and permanent hypertension in part due to heredity and in part acquired, as time goes on, from a variety of causes. He gives an excellent description of the changes which may occur from hypertension in the large vessels, in the retinal vessels and in the capillaries and discusses methods of treatment, using illustrative reports of cases to enliven his thesis.

Hypotension is taken up in much the same manner. Hypotension is considered as being either congenital or acquired; what may be done in the treatment of low blood pressure is described.

The book is interestingly put together and is written from a combined clinical, pathologic and physiologic point of view. It contains an excellent list of references to current literature. On the whole, this work is well worth reading and will prove especially valuable to clinicians interested in vascular disease and its management.

Stoffwechselprobleme. By S. J. Thannhauser. Berlin: Julius Springer, 1934.

This small book contains five lectures on the following topics: (1) the structure of nuclear material in plants and animals and the metabolism of nucleins, (2) the chemistry of the pigments of the blood and bile, (3) the place of formation of biliary pigment, (4) the production of icterus and (5) the lipoidoses: xanthoma, Gaucher's disease and Niemann-Pick's disease.

The presentation is scholarly and critical; each lecture contains a review which brings the subject up to date by including the more recent contributions. Thannhauser is professor of medicine in Freiburg. He speaks with special authority in the fields of purine chemistry and bile. His "Lehrbuch," a monograph on metabolism and diseases of metabolism, is widely recognized as a masterpiece of medical writing in this field. The "Stoffwechselprobleme" is lacking in a bibliography, much to the disappointment of the reviewers.

Traité de physiologie normale et pathologique: Tome VII. Sang et lymphe, réactions d'immunité. Deuxième edition. Published under the direction of G.-H. Roger and Léon Binet. Price, Stitched, 100 francs; bound, 120 francs. Pp. 731, with 82 figures. Paris: Masson & Cie, 1934.

This treatise on physiology in eleven volumes has been so well received that it has been considered worth while to bring out a second edition. The present volume is the first of this edition that has appeared. It is considerably (229 pages) longer than the first edition. The following subjects have been particularly revised and amplified: the origin of the formed elements, hemorrhage, transfusion, blood chemistry, coagulation, immunity and anaphylaxis. The work is liberally documented with references to the literature, mostly French, although English, American and German works are cited as well. French science may well feel proud of this evidence of its vitality.

Reliefstudien an der normalen und Krankhaft veränderten Spieiseröhre. By Richard Schatzki. Pp. 149, with 159 illustrations. Acta radiologica, Supplementum XVIII, 1933.

This interesting monograph deals systematically with the roentgen appearance of various lesions of the esophagus. There are 159 reproductions of roentgenograms. These serve to illustrate the text, which deals not only with interpretation but with technic as well. There is a thorough bibliography.

Brucella Infections in Animals and Man: Methods of Laboratory Diagnosis. By I. Forest Huddleson. Pp. 108. The Commonwealth Fund, 1934.

This little monograph brings together in an interesting manner the available literature on the bacteriology of the Brucella group and deals especially with the methods of laboratory diagnosis. The technic of isolation of the organisms, the pathology of experimental infection and the biologic methods for identifying and separating various strains are described. The bibliography includes one hundred and eighty-eight titles; the illustrations are good, and there is an index.

Radiologie de la vésicule biliaire. By Nemours-Auguste. Price, 45 francs. Pp. 186, with 102 figures and 27 plates. Paris: Masson & Cie, 1934.

This book is in line with the French custom of monographic treatment of highly restricted subjects. One would hardly think that there was enough to say about the roentgenology of the gallbladder to fill a whole volume, and still one finds here surprisingly little superfluous matter. The subject is taken up from every possible angle. Especially valuable are the numerous excellent reproductions of roentgenograms and diagrams. The book should prove a storehouse of information not only for roentgenologists but also for physicians in general. There is a thorough bibliography, with good representation of the American literature.